Phase III Clinical Study of Allogeneic Stem Cell Transplantation with Reduced Conditioning (RICT) versus Best Standard of Care in Acute Myeloid Leukemia (AML) in First Complete Remission

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TABLE OF CONTENTS

Introduction

This is a protocol amendment to the academic trial conducted by the Transatlantic Leukemia Study Group (TRALG) in cooperation with the Canadian Blood and Marrow Transplantation Group. The pertinent changes and updates to the protocol are outlined and justified in the protocol.

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3. DEFINITIONS AND ABBREVIATIONS

AML is defined according to the recent World Health Organization classification (WHO 2008).

AML risk categorization[1]
Good risk AML: Any patient with favorable cytogenetic abnormalities — t(15;17), t(8;21) or inv(16)(p13q22), irrespective of marrow status after first induction course or the presence of other genetic abnormalities or if the AML is assessed as secondary AML. Patients with normal karyotype and presence of the molecular genetic combinations FLT3-/NPM1+, or FLT3-/CEBPA double mutated) are also considered low risk.
Intermediate risk AML: Any patient not in either good or poor risk groups.
Poor risk AML
• More than 15% blasts in the BM after first induction course and not favorable cytogenetics
• Adverse karyotype (-5, -7, del(5q), abn(3q), complex), and not favorable cytogenetics
• Monsomal karyotype, as defined by Breems et al (2008)
• Secondary AML, ie AML without favorable cytogenetics, following an antecedent hematological disease, *or* AML following treatment with mutagenic drugs or irradiation.

Complete remission. The bone marrow is regenerating normal hematopoietic cells and contains <5% blast cells by morphology in an aspirate sample with at least 200 nucleated cells with no Auer rods. ANC should be more than 1.0 x 10^9/L and platelet count >100 x 10^9/L.

Complete Remission with incomplete recovery (CRi): Fulfilling all criteria for CR except for residual neutropenia (<1000/μL) or thrombocytopenia (<100,000/μL). Patients fulfilling the criteria of CRi, who receive post-remission therapy before full recovery of blood counts will also be accepted as having achieved CR.

Overall survival (OS) is defined as the time interval between the date of inclusion and the date of death from any cause. Incomplete data resulting from patients who are lost to follow-up or who withdraw their informed consent will be censored at the date they were last known to be alive. Patients who have not died prior to study termination will be censored at the latest date known to be alive.

Non-relapse mortality. Death during continuous CR1

Relapse is defined as 5% or more blast cells in the bone marrow, not secondary to regeneration after myelosuppressive therapy; extramedullary leukemia, or the persistence of blasts in PB.

Disease-Free Survival (DFS) is the time between date of inclusion and date of relapse or death from any cause.

Registration. Patients are registered for the study when a registration form has been sent to, and is approved by, one of the national PIs. The *Registration Form* is a document confirming that the investigator and her/his patient have agreed to aim for a reduced intensity conditioning transplant (RICT) performed in accordance with Amendment #2 of the TRALG-01 study protocol, applying the routines for donor search and donor selection outlined. The registration form should be sent before any donor search is initiated. Patients can be registered for the study before attained CR1. See Registration Form with comments (Appendix X) and protocol section 7.

Inclusion. To be formally *included* in the study, patients should have attained CR1 and fulfill inclusion and exclusion criteria. The date of inclusion is the date of HLA typing of the first potential sibling donor, or the date of sending a search request to a donor registry. These dates, and the date of confirmed CR1, will be retrieved in CRF Part I. For details, see protocol section 7.

[1] These criteria might be incomplete or obsolete at the time of study analyses. Original lab reports from cytogenetics, FACS and molecular genetics will be retrieved to make possible a retrospective refined risk categorization.

Treatment Assignment is the allocation, based on the results of donor HLA typings, of a patient to one of the study groups.

HLA match. *A matched sibling donor* (MSD) is identical on Class I (HLA-A, -B; serological typing), and HLA-DRB1 (genomic typing). If there are homozygotic antigens on Class I, high resolution typing should also be performed to exclude mismatch on the allelic level.
For the purpose of this study, a *matched unrelated donor* (MUD) is identical on HLA-A, –B, and DRB1 (allelic level). One single allel mismatch is permitted on HLA-C.

Potential sibling donor is a sibling without apparent contraindications to G-CSF mobilization and stem cell harvest and who is willing to undergo HLA-typing.

Study Groups. In this study, patients will be allocated to *either* allografting (from a matched sibling donor (MSD/RICT group), matched unrelated donor (MUD/RICT group) *or* standard of care (MSD/Control, MUD/Control). See Flow Chart, Appendix XI. For the statistical analyses of study endpoints, these groups will be used and weighed according to the statistical plan, see section 11. In the protocol text, for the sake of convenience the Control groups (MSD/Control and MUD/Control) and RICT groups will be referred to by the terms "Control group" or "RICT group", respectively.

Suitable donor is a HLA-identical sibling who has signed the Informed Consent for Donors (Appendix III) and after medical work-up has been found fit to undergo G-CSF mobilization and PBSC harvest, or BM harvest.

Minimal Residual Disease (MRD) designates the existence of cells belonging to the malignant clone in an amount below what is detected morphologically. The smallest MRD detectable is defined by the laboratory performing the analysis.

Complete donor chimerism is the presence of >95% donor cells in PB. **Mixed donor chimerism** is the detection of 5-95% donor in PB.

Rejection is either lack of initial donor engraftment *or* the development of pancytopenia and marrow aplasia after intial engraftment *or* the recurrence of host hematopoiesis with <5% donor T-cells.

Abbreviations

AE	Adverse Event
aGvHD	Acute Graft-versus-Host Disease
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
AP	Alkaline phosphatase
AST	Aspartate Aminotransferase
ATG	Anti-Thymocyte Globulin
BM	Bone Marrow
cGvHD	Chronic Graft-versus-Host Disease
CMV	Cytomegalovirus
CR	Complete Remission
CRF	Case Report Form
CSO	Central Study Office
CTCAE	Common Terminology Criteria for Adverse Events (CTCAE)
CyA	Cyclosporine A
DFS	Disease-Free Survival
DLI	Donor Lymphocyte Infusion
EORTC	European Organization for Research and Treatment of Cancer
FISH	Fluorescent In Situ Hybridization
ISCN	International System for Human Cytogenetic Nomenclature (1995)
GvL	Graft-versus- Leukemia

HLA	Human Leukocyte Antigen
HSC	Hematopoietic Stem Cell
HSV	Herpes Simplex Virus
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAb	Monoclonal Antibody
MMF	Mycophenolate Mofetil
MRD	Minimal Residual Disease
NRM	Non-Relapse Mortality
NSO	National Study Office
OS	Overall Survival
PB	Peripheral Blood
PBMC	Peripheral Blood Mononuclear Cells
PBSC	Peripheral Blood Stem Cells
PLT	Platelets
RF	Registration Form
RIC	Reduced Intensity Conditioning
RICT	Reduced Intensity Conditioning Transplant
SAE	Serious Adverse Event
SC	Stem Cells
SCT	Stem Cell Transplantation
Tx	Transplantation or Date of Transplantation
ULN	Upper Limit of Normal
MSD	Matched Sibling Donor
MUD	Matched Unrelated Donor
QoL	Quality of Life
UPN	Unique Patient Number
WBC	White Blood Cell count

4. BACKGROUND

Incidence and prognosis of AML

The incidence of AML in Sweden is around 4/100 000 per year with a median age at diagnosis of 71 years. Only 27% of patients are <60 years. Progress in therapy and supportive care has led to gradual improvement in the overall results in younger individuals but the prognosis in elderly patients is unchanged and still very poor (Figures 1 and 2).

Most important poor prognostic features in AML, determining the ultimate outcome of therapy, are adverse cytogenetics, secondary AML and refractory disease. Patients with the cytogenetic abnormalities t(15;17), inv(16) and t(8;21) constitute a small group (10-15%) with a prognosis much better than average (Burnett et al, 2002a, Döhner et al, 2009).

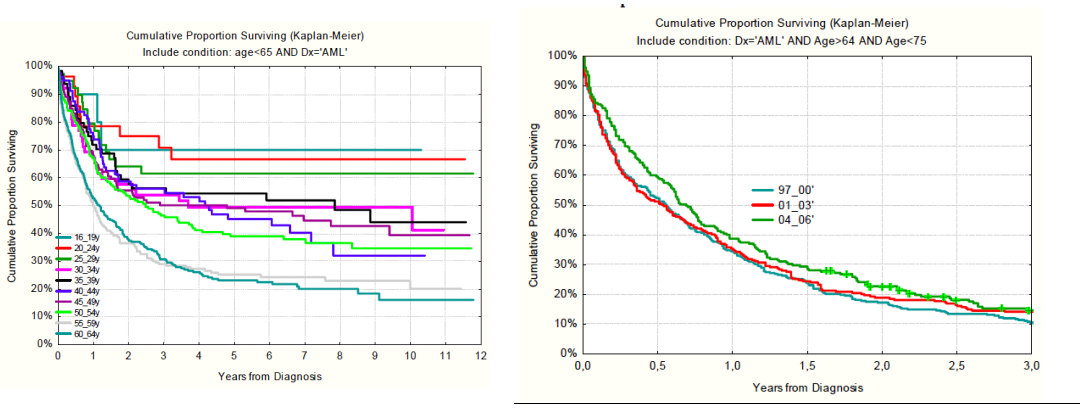

Figure 1 and 2. Overall survival from AML diagnosis of Swedish patients, <65 years (left) and 65-74 years (right) diagnosed 1997-2006. Data from the Swedish National Registry of Acute Leukemia in Adults (Juliusson G, 2010).

Allogeneic stem cell transplantation

Allogeneic stem cell transplantation (allo-SCT) is an established treatment modality for many bone marrow malignancies, such as AML (Butturini & Gale, 1994). Traditionally, allo-SCT has consisted of a myeloablative preparative regimen (conditioning) using supra-lethal doses of chemotherapy with or without total body irradiation (TBI), followed by infusion of allogeneic bone marrow (BM) or peripheral blood stem cells (PBSC). It was previously assumed that myeloablation was the most important component of the procedure and the stem cell infusion was considered as rescue from the lethal effect of the conditioning regimen on the patient´s bone marrow. However, it has become clear that the low relapse rate after allo-SCT to a substantial extent is due to a graft-versus-leukemia (GvL-) effect exerted by immunocompetent donor cells (Horowitz et al 1990). A striking example of the importance of this effect is demonstrated in a registry study where outcome after "myeloablative" allo-SCT in AML was studied with regard to donor type. The relapse rate in patients who were transplanted from a monozygous twin as the donor was 52%, whereas relapse rate after an HLA-identical sibling transplant was 16% (Gale et al, 1994).

Non-relapse mortality and Graft-versus-Host disease

Unfortunately, the benefit of allografting, ie the consistently observed reduced relapse rate, occur at the cost of a high procedure-related toxicity and non-relapse mortality (NRM) leading to treatment failure rates of the same order of magnitude for the three treatment modalities – chemotherapy, autograft, allograft - applied in AML. Indeed, based on results from previous large studies using "genetic randomization", the (Zittoun et al, 1995; Cassileth et al, 1998; Burnett et al, 2002b), the value of allo-SCT in AML have been questioned (Burnett, 2002b, Goldstone & Avivi 2002). However, a large retrospective study clearly demonstrated a beneficial effect of allo-SCT from sibling donors in CR1 in both the intermediate and high risk category, but only in patients below the age of 40 years (Cornelissen et al, 2007).

The Graft-versus-Host Disease (GvHD), mediated by donor T-cells, is the most common non-infectious complication after allo-SCT. Severe GvHD (grade III-IV) occurs in 10-15% of patients after conventional allo-SCT and is associated with a high mortality. Established risk factors for GvHD are

high age of patient and/or donor, the combination of female donor and male patient, HLA-mismatch between donor and patient, and the use of very toxic preparative regimens.

Current indications for allo-SCT in AML
Current recommendations for patients with AML used in most centers are to offer myeloablative allografts to high or intermediate risk younger patients in first remission (CR1), provided they have an HLA-identical sibling donor and are in otherwise good health. For younger high-risk patients, a transplant also from an unrelated donor could be considered. Thus, age and/or co-morbidities and the expected risk of NRM limit the use of myeloablative allografting in the majority of AML patients. For example, only approximately 10% of Swedish AML patients aged 50-70 years underwent allo-SCT 1997-2008 (Juliusson G, 2010).

Rationale for the use of reduced intensity conditioning
In the light of the high NRM after myeloablative allo-SCT and the importance of the GvL-effect for disease control, the concept of "non-myeloablative" or "reduced intensity" conditioning has been proposed as a mode of improving results of allo-SCT (Slavin et al, 1998). Using this technique, patients receive a preparative regimen that may not result in irreversible marrow suppression, but still produces enough immunosuppression to allow engraftment of donor stem cells. It is assumed that donor T lymphocytes once established will eradicate residual disease.

An observation supporting the rationale for the use of RIC originates from the therapeutic potential of donor lymphocyte infusions (DLI) to eradicate remaining, or reappearing malignant host AML cells (Slavin et al 1995, Porter et al, 2000).

The significant advantage of the new technique is the reduced toxicity of the preparative regimen and the possible decrease in incidence and severity of acute GvHD. Therefore, it is possible to use this treatment modality in patients who due to age or comorbidities otherwise would be excluded from having an allo-SCT.

RICT in AML, Clinical results
Several recent retrospective studies suggest that RICT in elderly patients with AML may improve outcome compared to standard chemotherapy, albeit the prolonged LFS does not always translate into a prolonged OS due to a high NRM in patient aged 60-70 years (Farag S et al Blood 2011). In a donor *versus* no donor study, Mohty M et al (2005) demonstrated that a RIC from a MSD improved prognosis in elderly AML patients. Additional support for the notion that RICT using both MSD or MUDs may improve prognosis in elderly AML are discussed in a recent review (Gupta V et al 2010). Preliminary results from an interim analysis of the present study (n=101), using only MSDs, demonstrated a low NRM (14%) and a trend towards a lower relapse rate in the RICT arm (Kiss et al, 2010).

RICT in AML, conditioning regimens
Many centers have commenced small trials using a variety of protocols for reduced intensity conditioning. In addition to fludarabine, which is universally used as immunosuppressive agent in the RIC setting, the regimens described contain variable amounts of chemotherapy. One, almost purely immunosuppressive conditioning is the regimen based on low-dose (2 Gy) total body irradiation and fludarabine developed at the Fred Hutchinson Cancer Research Center in Seattle (McSweeney et al, 2001). Using this protocol, the cytopenia typically is very mild and more than 50% of patients do not need platelet transfusions during the transplant period. In contrast, the Jerusalem group pioneered RIC transplants using a more myelotoxic protocol containing 8 mg/kg busulphan, fludarabine and ATG (Slavin et al, 1998). Additional RIC approaches are the melfalan/fludarabine/alemtuzumab combination used in the UK (DasGupta et al, 2007), and the German FLAMSA-RIC protocol (Marks et al, 2008).

RICT in AML, sibling donor or unrelated donor
A number of recently published retrospective studies have demonstrated that the non-relapse mortality after matched unrelated donors (MUDs) are similar to what is seen after matched sibling donor (MSD) transplants (Schetelig J, et al 2008; Gupta V, et al 2010). Also, in a large retrospective study, MUD

RICT was found to be feasible in elderly patients (Ringdén O et al 2009). These findings open the possibility to include MUDs in the present study. The more potent graft-versus-tumor effect exerted by MUD allografts may even reduce the risk of leukemia recurrence compared to allograft from a MSD.

However, the detrimental consequences of acute and chronic GvHD, and its treatment, in elderly patients call for special caution with respect to donor selection. A single C antigen mismatch, but not an allell, was recently shown to be associated with inferior outcome (Woolfrey et al, 2011). This finding is in accordance with results in a previous study (Lee SJ et al, 2007), and further bolstered by results in a recently published study from the NMDP (Passweg et al, 2011). Based on these studies, for the purpose of this study a "matched" unrelated donor (MUD) will be matched for =8/8 loci, defined as identity on HLA-A, -B, C and -DRB1 (allelic level), whereas one single allel mismatch on HLA-C is permitted (≥7/8 match). If DQ typing is performed a DQ mismatch in conjunction with an HLA C allelic mismatch (=8/10 match) is not allowed. If an acceptable MUD is not identified, the patient will be allocated to the control group and treated according to institutional practice.

Rationale for a controlled study using RICT in AML

So far, there are no reports from controlled prospective studies comparing reduced conditioning transplants with conventional allo-transplants or with standard chemotherapy. Yet, the new technique is already established in most transplant centers. The initial good clinical results and the attractiveness of the concept has stimulated investigators to launch numerous phase 1 and phase 2 studies in leukemias, lymphomas, multiple myeloma and solid tumors. The need for prospective validation of RICT in AML was recently pointed out in a review article (Gupta V, et al. 2011). Below are listed the arguments for a prospective, controlled study in AML comparing RICT (MUD or MSD) with standard of care.

- Long-term survival of elderly ML-patients is poor and has not improved.
- Myeloablative allografts in elderly patients is associated with an unacceptable NRM
- Immunological mechanisms are important in disease control after allo-SCT.
- RIC transplants in AML are feasible with moderate NRM. Clinical results are promising.
- The RICT concept is already implemented in the clinic and increasingly used as a potentially curative treatment in elderly or otherwise frail AML patients. Many centers are familiar with the procedures.
- There are no prospective studies comparing RIC transplants with standard of care.
- Recent data indicate that MUDs and MSD render similar results after RICT.

RICT in AML, summary

Available data suggest that RICT from MSD or MUD in elderly patients with AML, are feasible, and that toxicity between MSD or MUD appears similar. RICT appears to be a powerful antileukemic treatment also in elderly patients. Yet, transplantation still is associated with an increased NRM compared with standard chemotherapy. Whether the decreased relapse rate related to RICT translates into improved OS, in face of an increased NRM, has not yet been established. This protocol will attempt to determine differences in OS between elderly patients with AML receiving either a RICT or treatment with a non-transplant approach.

Comments on study design

Registration and Inclusion procedures: In order to avoid bias due to patient selection, patients can be *registered* for the study only prior to HLA-typing of a potential sibling donor, or the search for a MUD, and *included* only after attained CR1. Details of the procedures are provided elsewhere in this protocol.

Heterogeneous treatment policies: The paramount idea behind this study is to study the outcome for AML patients when using the procedure of RICT as compared to the standard procedure of chemotherapy. Therefore, the protocol does not prescribe details of the consolidation regimens or the duration of treatment for patients in the Control groups. Nor is one specific conditioning regimen mandatory, and some variation is permitted with respect to post-transplant immunosuppression. However, each site is advised not to change the conditioning regimen during the study.

Consequently, the results of this study will mirror AML treatment as practiced during the study period. In the final analyses, it will be possible to analyze the endpoints by country or by regimen used. Patients in the Control groups may be enrolled in other post-remission studies.

Conclusion

RIC transplant in AML, also in elderly patients, is feasible and is associated with a low rejection rate. Available data indicate that (i) the non-relapse mortality (NRM) is lower than after conventional allo-SCT; (ii) relapse rate is reduced compared to standard chemotherapy, and (iii), only prospective trials can give the answer whether RICT does improve survival comopared to standard chemoterapy.

In terms of overall survival and NRM, results of RICT using MUDs seem similar to MSD/RICTs. Consequently, this amended protocol permits the use of MUDs, defined as 8/8 or 7/8 match (only one HLA-C allel mismatch permitted).

In summary, RICT has, without solid scientific foundation, quickly become a widespread treatment option for elderly patients with AML. There is a need for a controlled prospective study evaluating RICT to standard of care with respect to survival, and – importantly - quality of life.

5. OBJECTIVES AND ENDPOINTS

Primary Objective and Endpoint
The *primary objective* of this study is to determine in a group of elderly AML CR1 patients with a potential matched sibling donor (MSD) whether a reduced intensity conditioning transplantation (RICT) leads to a superior overall survival compared to standard of care.
Primary endpoint is Overall Survival

Secondary Objectives and Endpoints

1. *Objective*: To determine in the group of elderly AML CR1 patients without a MSD whether a matched unrelated donor (MUD) RICT leads to a superior overall survival compared to standard of care. *Endpoint* is Overall Survival.
2. *Objective*: To determine whether RICT from any donor (MSD or MUD) leads to superior overall survival compared to standard of care. *Endpoint* is Overall Survival.
3. *Objective*: To determine differences in DFS, NRM and QoL in the groups defined above. *Endpoints* are Disease-free survival, causes of death and Quality of life (as assessed by the EORTC QLQ-C30 instrument).

Further to study in transplanted patients

- *Graft-versus-Host Disease*. Incidence and severity of acute and chronic GvHD
- *Chimerism analyses*. Impact on outcome of T-cell chimerism at D +30 and +100.
- *Clinical results,* with respect to different AML risk categories, and pre-transplant patient and allo-SCT risk index.

Importantly, the primary study objective in the original protocol has not been modified in the present amendment.

6. TRIAL DESIGN

Description of the study (Flow chart, Appendix XI)
This is a multi-center phase III prospective study applying HLA-based allocation of patients to RICT, or to standard of care. The study will be performed according to GCP guidelines. Study population encompasses AML patients, 51-70 years, in CR1 with an indication for allo-SCT but for whom a full myeloablative conditioning is not advisable due to age and/or medical impairment.

To prevent patient selection bias, HLA typing of siblings or initiating MUD search *should not be performed prior to patient registration* and signed informed consent. The statistical analyses rely on comparisons between patients with identified donors (MSDs or MUDs), and patients for whom the donor search was not successful. For details, see Selection of Subjects, and Statistical Considerations. There will be three defined groups of AML CR1 patients, each contributing to final analyses.

1. One group comprises patients with at least one potential sibling donor, for whom there is no indication for MUD search in case the sibling(s) are not HLA identical - or otherwise not eligible for HSC donation.
2. One group comprises patients with at least one potential sibling donor, and for whom there is an indication and intention to proceed for a MUD search in case the sibling(s) are not HLA-identical or otherwise not eligible.
3. One group comprises patients without potential sibling donor, but for whom there is an indication to go for a MUD search.

Treatment
Details on treatment of patients, including conditioning and immunosuppressive regimens are given in the Treatment of Subjects section.

• Patients allocated to any of the Control groups will receive conventional consolidation therapy according to local routines or guidelines. Inclusion in post-remission or maintenance studies is permitted.

• Patients assigned to one of the RICT groups, will typically receive a total of 2 (-3) chemotherapy courses before conditioning. It is recommended that RICT should be performed as soon as possible, and not later than 6 months after diagnosis. It is also recommended that a fruitless MUD search should be called off not later than after 4 months.

Follow-up
Patients in both groups will be followed for survival, relapse and quality of life for a minimum of two years. Also, once a patient has been included, it is essential to have details of the subsequent course of events, even if the assigned therapy never was carried out. Registered patients who do not achieve CR1 will be followed for survival only.

Statistical analyses
See Section 11 “Statistical Considerations”.

7. SELECTION OF SUBJECTS

News in this amended protocol

The timing of inclusion of patients in this study is of critical importance for the ability to interpret the final results. The study will be evaluated on an intent-to-treat basis and all patients included will be part of the analyses. In this amendment, two important changes have been introduced both of which is affecting the inclusion process. The rationales for these changes are given in the Background section.

1. In the original protocol, inclusion was only permitted after attained CR1, and the date of HLA-typing of the first sibling was defined as the inclusion point. In this amended protocol, patients can be *registered* for the study - and donor search started - before attained CR1. *Inclusion* in the study requires achieved CR1. The formal inclusion date is when donor search is initiated (blood sampling from the first sibling, or the dispatching of a MUD search), *or* the data of CR1 (for patients registered before achieved remission). Registered patients not achieving CR will not be formally included in the study, but will be followed for survival.
2. In this amended protocol, the recruitment base is widened to patients fit also for RICT from MUDs. The accompanying implications and complications for the study design and statistical analyses are described elsewhere in the protocol, see Treatment Assignment (below) and Sections 6 and 11. Importantly, in order to avoid the deleterious effects of GvHD in elderly patients only 7/8 (one C-allel mismatch), or 8/8 matched unrelated donors are accepted. It is expected that a ≥7/8 MUD will be found for 50-60% of patients. If a ≥7/8 donor is not identified, the search shall be terminated, and the patient allocated to the Control group. The point of calling off a fruitless MUD search is at the investigators discretion, and the date will be retrieved in the CRF. Patients relapsing, or otherwise becoming unfit for the procedure, before a MUD is identified and medically approved will be allocated to the Control group, see Section 11.

Study population

Patients 51-70 years of age with AML, intermediate or poor prognosis (see Definitions) for whom there is no indication for allografting with myeloablative conditioning will be approached.

It is expected that the majority of patients will be registered for the study after attaining CR1. However, patients not yet in CR but fulfilling some (*see below*) other inclusion and exclusion criteria may also be registered (see Registration Form, Appendix X). This situation may occur e g whenever there is clinical haste due to a high risk disease, or donors´ geographical availability.

Patients will be informed about the study, and asked if they accept the treatment proposed in this study as a consequence of HLA typings. By signing the informed consent, the patient accepts registration for the study, and that achieving CR1 is a prerequisite for formal inclusion and subsequent treatment as stated in the protocol.

Inclusion Criteria[1]

1. AML of intermediate or poor prognosis (see Definitions)
2. Age 51 – 70 years.
3. Achieved CR1 or CRi
4. Indication for a RIC but not a myeloablative alloSCT.
5. Judged to be able to tolerate a RICT if a suitable donor (MSD and/or MUD) is found.
6. Judged to be able to tolerate further standard consolidation chemotherapy.
7. Willing to undergo a RICT if a suitable donor is found.
8. Signed informed consent.
9. Willing and able to comply with protocol requirements.
10. Registration Form (Appendix X) filled in and sent before initiation of donor search.

[1] Comments on Inclusione criteria (IC): #1 Pts can be registered before final risk categorization (e.g. if cytogenetical analysis is delayed). IC # 3. Registration is permitted before CR.

Exclusion Criteria[1]

1. AML with good risk features
2. Planned to receive full dose conditioning
3. Initiation of donor search performed before registration in the study
4. Additional malignancy that might interact with the endpoints of the study
5. Serum creatinine > 2 x the ULN, or abnormal liver function; ALT or AST > 3 x ULN
6. Other severe concurrent illness

Registration and Inclusion process

The inclusion procedures differ depending on whether or not there are potential sibling donor(s).

Patients with at least one potential sibling donor

• A potential sibling donor is a sibling without apparent contraindications to G-CSF mobilization and stem cell harvest, who is willing to undergo HLA-typing. It is recommended to briefly inform siblings about the study at an early stage, and ask if they are willing to be HLA-typed. Note that siblings with evident contraindications to G-CSF and PBSC collection, or BM harvest, are not considered "Potential Sibling Donors" and should not proceed to HLA-typing.

Note:
• HLA typing of the *patient* may be performed at any point, e g at diagnosis.
• Patients can be registered for the study *before or after* attained CR1.
• Registration (Appendix X) of the patient must precede HLA typing of a potential sibling donor.

Procedures, see Registration Form (Appendix X)

1. Check Inclusion & Exclusion Criteria.
2. Patient´s signed informed consent.
3. Fill in and send the RF to the NSO. Note the important paragraph **6b**.
4. The NSO confirms eligibility, formally registers the patient and faxes the RF back.
5. HLA-typing of sibling(s). To avoid selection bias, all potential sibling donors should preferably undergo HLA-typing. The date of drawing blood from the first sibling is defined as the *Inclusion point*[2].
6. *If a sibling is HLA identical*, she/he has to sign the Donor`s Informed Consent (Appendix III). Thereafter, medical work-up of donor and patient should be performed as per local practice and the transplantation undertaken as soon as possible.
7. *If sibling(s) are not HLA identical* (or if unavailable due to eg medical infirmity) – proceed in line with previous decision at registration, see RF paragraph 6b.
   - If the answer was *No ("no MUD search planned if sib(s) unavailable")*, the patients will be treated as per local practice.
   - If the answer was *Yes ("MUD search planned if (sib(s) unavailable")*, a ("secondary") MUD search should be initiated, see below (procedure 5 and onwards).

Patients without a potential sibling donor

Note:
• HLA typing of the *patient* may be performed at any point, e g at diagnosis.
• Patients can be registered for the study *before or after* attained CR1.
• Registration of the patient must precede the date of dispatching a request for a MUD search.

Procedures (see Registration Form; RF)

1. Check Inclusion & Exclusion Criteria
2. Patient´s informed consent.
3. Fill in and send the RF to the NSO.

[1] Exclusion criteria #5 and #6, if judged as temporary, do not exclude pt from registration in the study.
[2] Patients registered before CR but who do not eventually attain remission will not be formally included in the study (see "News in this amended protocol" above.

4. The NSO confirms eligibility, formally registers the patient, and sends the RF back.
5. Dispatch MUD search request.
7. If a MUD is identified, the patient should undergo RICT as soon as possible.
8. If a MUD is not identified, the patient is allocated to MUD/Control group and treated as per local practice.

Treatment assignment

1. Treatment assignment is the allocation of patients to study groups and is based on the results of HLA-typing of siblings and/or of MUD search. The MUD search could be performed as a *primary* procedure for patients without a potential sibling donor, or as a *secondary* procedure for patients with siblings not eligible as donors. Any patient with an *identified and medically approved* donor will be allocated to the RICT group, whereas patients without such a donor will be allocated to the Control group. This approach has consequences also for treatment assignment of patients whose donor search will be called off for reasons other than just failure to find a donor (see below).

2. If a MSD search is called off due to patient´s refusal, relapse, death or medical infirmity before the identification of a *HLA identical, medically approved* sibling donor, the patient is allocated to the Control group, whereas patients with an identified and medically approved MSD will be assigned to the RICT group, also if the transplant was not undertaken.

3. If a MUD search is called off due to patient´s refusal, relapse, death or medical infirmity before the identification of a medically approved MUD, that patient will assigned to the Control group, whereas patients with an identified medically approved MUD will be allocated to the RICT group, also if the transplant was not undertaken.

To be able to accomplish the treatment assignment, i.e. strictly allocate patients to study groups and perform statistical analyses, the following dates will be retrieved in the CRF.

Patients with a potential sibling donor

- Dates of CR1 and initiation of MSD search blood sampling for HLA typing of the first potential sibling donor (*Inclusion point #1*).
- Date of clinician´s decision whether to accept or not accept (based on HLA typing and medical work-up, etc) one of the siblings as a donor (*Treatment Assignment point #1*).
- Date of calling off the MSD search.
- For patients planned for a secondary MUD search: Date of initiation of MUD search (*Inclusion point #2).*
- Date of receiving a medical approval of an identified MUD, *or* the date when donor search for any reason is called off *(Treatment Assignment point #2).*

Patients without a potential sibling donor

- Dates of CR1 and initiation of a MUD search (*Inclusion point).*
- Date of receiving a medical approval of an identified MUD*, or* when MUD search for any reason is called off *(Treatment Assignment point).*

8 TREATMENT OF SUBJECTS

During the period after registration but before treatment assignment, patients will be treated as per local practice. After treatment assignment, patients in the Control (no transplant) group will be treated as per local practice, whereas patients with an identified and medically approved donor will proceed to RICT.

MSD/Control and MUD/Control groups
After treatment assignment, patients assigned to Control group will receive conventional consolidation therapy according to institutional practice or within studies of post consolidation therapy. It is presumed that patients in the Control group will receive a total of 3-4 chemotherapy courses. Relapsed patient in the Control group will be treated at the discretion of the clinician, but the patient will be followed and reported within the study for survival. Relapsed patients may receive any salvage treatment.

MSD/RICT and MUD/RICT groups
Patients allocated to RICT group should proceed as soon as possible to transplant as the next treatment after achieved remission. Due to medical or logistic factors, consolidation course(s) according to institutional practice may be given. Consequently, patients in the RICT group will (before conditioning) receive a total of 1-3 chemotherapy courses.

If a patient in the RICT group relapses, or if a contraindication to the assigned treatment occurs, the patient will be treated at the discretion of the clinician, but nevertheless reported within the study.

Donor´s consent and medical work-up
Siblings may be approached and informed about the study at any time. However, no blood sampling or medical work-up except a brief medical history, may be obtained before the patient has signed the consent form and been registered on the study. If a sibling proves to be HLA-identical to the patient, the sibling should be informed and asked for her/his informed consent (Appendix III) to undergo medical work-up and donate PBSC or BM. Medical work-up of the donor will be performed according to institutional practice.

Contraindications to G-CSF mobilization and PBSC harvest include serious cardiopulmonary, renal, infectious, hepatic, mental, malignant, immunologic, or other systemic disease. Donor must have adequate venous access for leukapheresis, or agree to placement of central venous catheter (femoral, jugular, subclavian). PBSC from donors may be harvested and cryopreserved prior to infusion to ensure a sufficient number of stem cells. BM as the source of stem cell may be used as per the choice of the donor.

Patient´s pre-transplant work-up
Patient´s medical condition and remission status should be evaluated within four weeks prior to the transplantation date. The pre-transplant work-up should be performed as per local standards. Some data will be retrieved in the CRF:
- CMV and EBV status and blood group (AB0, Rh).
- Bone marrow aspirate for remission assessment (*copy of lab report*).
- HLA typing (*copy of lab report*).

Mobilization and collection of donor PBSC
Mobilization and collection of donor PBSC will be performed according to institutional practice. Typically, G-CSF will be administered at a dose of 5 μg/kg (ideal body weight) bid.

Preferably, between 3.0 and 7.0 x 10^6/kg CD34+ cells will be collected and infused to the patient, target dose is 5 x 10^6/kg. No *in vitro* manipulation of the PBSC will be performed. Aliquots of the graft may be frozen and used for later DLI.

BM harvest could be performed as per local standards. Typically 3 x 10^4 MNC/kg will be harvested.

Conditioning Regimens

The paramount question of this study is whether RICT results in a superior survival compared to standard consolidation therapy in elderly AML-patients. Therefore, it is not felt necessary to prescribe only one conditioning regimen. On the contrary, both patient safety and study accrual might benefit if individual centers may use their ingrained routines. The conditioning regimens described below have been used in many patients and they contain a reasonable portion of chemotherapy to reduce the tumor burden, thereby hopefully preventing relapse until the GvL-effect is operative. Centers may select any of the conditioning regimens described below and are then asked to consistently use the chosen regimen. Note that busulphan may be given intravenously or orally as per center preference. Intrathecally administered methotrexate will be given to selected patients as per center routine.

As fludarabine is metabolized partly by a renal mechanism (Malspies Sem Oncol 1990), doses of fludarabine need to be modified if the calculated or assessed renal clearance is below the lower limit of the normal range.

Busulphan (orally *or* IV) and fludarabine

- Fludarabine 30 mg/sqm iv infusion over 30 min
  - on day –8 to day – 4 (=five days) for MSDs
  - on day -9 to day -5 or -4 (= five or six days) for MUDs
- Busulphan may be administrated orally or intravenously.
  - Orally. Total dose 8 mg/kg, given as eight doses of 1 mg/kg each on day –4 (two doses), day –3 (four doses) and day –2 (two doses).
  - Intravenously[1]. Total dose of Busulphex® is 6.4 mg/kg given as two doses of 3.2 mg/kg each, administered over 3 hours, on days -3 and -2.
- In-vivo T depletion with ATG, or alemtuzumab, as per local standards is permitted for MUDs

There shall be an interval of ≥ 8 hours between fludarabine and busulphan, and 48 hours between last dose of busulphan and infusion of stem cells.

Fludarabine, carmustine, melfalan

- Fludarabine 30 mg/sqm IV infusion over 30 min q d days –8 to -5 (four days)
- Carmustin 150 mg/sqm IV infusion over 60 min q d, days –7 and –6 (two days)
- Melphalan 110 mg/sqm IV infusion over 30 minutes on day –2.
- Alemtuzumab 10 mg (total dose) SQ on day -1.

There shall be an interval of 48 hours between melfalan and the infusion of stem cells.

Supportive measures post transplant

Supportive measures listed below represent basic general recommendations. In principle, centres are free to follow their local standard guidelines.

• *Blood transfusion support*. Red blood cell and platelet transfusion support will be given using standard procedures at each institution. Blood products should be irradiated and filtered.

• *Antibacterial prophylaxis*. As per center preference

• *Herpes simplex virusand varicella zoster prophylaxis*. As per center preference

• *Surveillance and pre-emptive treatment of CMV*. Test for CMV antigenemia or PCR assay should be performed weekly from day 0, at least until D +100. If positive, appropriate treatment should be given.

• *Fungal prophylaxis*. As per center preference

• *P. carinii prophylaxis*. Trimethoprim-sulfamethoxazol at appropriate dose for a duration of at least one year.

• The use of G-CSF in the post-transplant setting should be individualized.

Immunosuppressive therapy

In the RICT setting, there are no data to support any claims of superiority of one regimen over another. All regimens in use at the participating institutions have been evaluated locally. It is not possible to mandate that one particular regimen should be used. Therefore, this protocol includes the use of either

[1] In case IV Busulphan is used, fludarabine doses can be moved one day closer to Tx.

methotrexate or mycophenolate mofetil (MMF) in addition to cyclosporine-A (CyA). It is however recommended that each center uses the same regimen throughout the study.

Cyclosporine-A (CyA)
The dose of CyA should be targeted and adjusted to a serum concentration as per center preference.

The first doses of CyA are given intravenously to try and ensure adequate levels at the time of transplant. If there is nausea and vomiting anytime during CyA treatment the drug should be given intravenously at the appropriate dose. Blood pressure, renal function tests (creatinine, BUN), electrolytes and magnesium need to be followed closely while receiving CyA at full dose.

In principle, cyclosporine should be given IV or orally in full dose from Day –1 until day 60, then be tapered, in the absence of GvHD, and stopped at day +120. However, if GvHD occurs, or if justified by chimerism data, CyA dose and duration should be individualized

CyA and short course methotrexate
This immunosuppression combination includes full dose CyA and methotrexate. The dose of methotrexate is 15 mg/sqm iv day 1, 10 mg/sqm day 3 and day 6. The use of folinic acid rescue on days 4 and days 7 –10 is optional. A fourth dose (10 mg/sqm) of methotrexate Day +11 with optional use of folinic acid rescue on day +12, should be added after MUD-RICT, or otherwise if the risk of GvHD is considered high.

CyA and mycophenolate mofetil (MMF)
This immunosuppression combination includes full dose CyA and MMF. For CyA-dosage and schedule, see above. The MMF dose, either orally or IV, is 15 mg/kg bid. Doses will be rounded to the nearest 250 mg (capsules are 250 mg). Most patients will receive 1000 mg bid.

• After MSD-RICT, and in the absence of GvHD, MMF will be given until day +50 post-Tx and then stopped without tapering.

• After MUD-RICT MMF will be given 15mg/kg q 8 hrs to day +40, then tapered to day +96.

If there is nausea and vomiting, preventing oral administration, MMF dose should be reduced accordingly, or administered intravenously.

GvHD, treatment
Acute GvHD (Appendix V), should be treated as per local routines with prednisone/prednisolone. In case of steroid-refractory GvHD, defined as progression after three days *or* no improvement after 7 days *or* incomplete response after 14 days of corticosteroid treatment, patients will be managed according to local practice or ongoing studies. Chronic GvHD will be treated according to local practice.

Chimerism analysis and immunological intervention
Most centers have developed routines for chimerism assessment and immunological intervention. Therefore, only some principles are stated and centers are free to use their own routines as to the rest.

For the purpose of this protocol, chimerism analysis should be performed at least in PB at +1 month, at D +100 and at 1 year in PB or BM. Extra assessments may be needed in case of remaining MRD or administration of DLI. It is recommended to assess chimerism in T-cells and myeloid cells separately. Remaining or reappearing of host myeloid cells may be used as surrogate marker for MRD. Immunological intervention such as CyA taper or DLI may be considered.

No recommendations could be given as to the use of MRD surveillance. Local or national routines for surveillance and intervention will be applied.

Some details on chimerism, DLIs (time point, indication, dose, clinical effect) will be captured in the CRF.

9. PATIENT ASSESSMENTS

Patients are registered on the study based on the data provided on the Registration Form. After registration, the next reporting points is when patient´s risk categorization and CR status are confirmed and donor search has been initiated (CRF Part I).

Registration Form (Appendix X). All patients.
Information to confirm eligibility and for eventual inclusion.

- Site and patient identification data.
- Date of diagnosis. Intention to RICT.
- Informed consent.
- Inclusion and exclusion criteria.
- Remission status.
- Potential sibling donor available.
- Planned for MUD search if potential sibling donor is not eligible.

CRF Part I. All registered patients.
This report should be sent to the NSO when the result of induction course(s) has been confirmed and preferably within a week after the initiation of donor search. The report collects background data for all registered patients and gives the basis for formal inclusion in the study.

- Patient´s medical history. Physical examination. Cytochemistry. Comorbidity index.
- Diagnostic data and risk category. BM-morphology, flow cytometry, cytogenetics and molecular biology (*lab reports*).
- Induction treatment.
- CR1 date (*if applicable*).
- Date of initiation of donor search.
- Quality of Life instrument (*to be obtained and sent when clinical situation is stable*).

Patients not achieving CR will not be included but followed for survival using a separate simple form.

CRF Part II. All included patients.
This report will collect the subsequent dates and events for all patients included in the study. For SAE reporting, see “Serious Adverse Events (SAE) Reporting”.

For patients in the Control group

- AML-specific treatment
- Relevant dates (see Section 7, Treatment Assignment)
- SAEs, relapse, treatment after relapse, survival
- Performance status and Quality of Life (Appendix IX) at 12 and 24 months post Inclusion, in non-relapsed patients only
- Days spent in hospital (first year after Inclusion)

For patients in the RICT groups

- AML-specific treatment
- Relevant dates (see Section 7, Treatment Assignment)
- Results of HLA-typings (*lab reports from pt and identified approved MSD or MUD*)
- Pre-transplant work-up. Donor and transplantation details
- Performance status and Quality of life at 12 and 24 months post Inclusion, in non-relapsed patients only
- Days spent in hospital (first year after Inclusion)
- SAEs, relapse, treatment after relapse, survival
- Acute and chronic GvHD (Appendix V)
- Significant and unexpected toxicity or complication
- Chimerism at 1 month, at D +100, and (preferably) at 1 year.

10. ASSESSMENTS OF EFFICACY AND SAFETY

Efficacy assessments

To avoid a potential risk of earlier detection of relapse in the RICT groups due to more frequent monitoring and contact with the study personnel, it would be desirable that the patients in the Control groups were monitored at similar intervals as the RICT patients. However, this might not be feasible and no exact intervals between hematology assessments are prescribed in this protocol, nor will such data be captured in the CRF. Taking the aggressive clinical course of AML into account, the impact of different clinical routines between the two study groups will be minor in the evaluation of endpoints. The analysis of primary endpoint – survival – will not be influenced by clinical procedures such as different schemes of hematology assessments in the study groups.

Risk categorization of AML differs over time and will change during the next few years. Therefore, in the present amended protocol no comprehensive definition of high risk disease is provided. Instead, inclusion criteria is "AML without good risk features", ie the three established cytogenetic abberations t(8;21), inv(16) and t(15;17), with the addition of normal karyotype in association with the molecular combinations of FLT3-/NPM1+ and FLT3-/CEBP (double mutation) . It is important to retrieve all original lab reports on cytogenetics, flow cytometry, morphology and molecular genetic analyses. These data will undergo central review at time of the final study analyses.

Relapse and survival
All patients will be followed for relapse and survival for a minimum of two years.

Bone marrow cytology
Bone marrow morphology will be used routinely in all patients for the establishment of remission.
• In the transplant group, marrow morphology will be performed at the pre-Tx work-up and at day +100 post-transplant. Otherwise, bone marrow morphology is to be obtained only when clinically indicated.
• In the Control group, marrow morphology is to be obtained only when clinically indicated.

Hematology
Hematologic assessments including hemoglobin, WBC, differential, and platelets will be documented in the CRF prior to Inclusion and as part of the pre-transplant work-up. In addition, it is presumed that, in all patients, hematology will be performed routinely prior to chemotherapy and at regular follow-up visits. These data will not be captured in the CRF.

Quality of Life
The changes and differences of Quality of Life (QoL) between transplanted and non transplanted patients will be assessed by use of the validated instrument QLQ-C30 from the EORTC (Appendix IX). For the purpose of assessing the impact of treatment on quality of life in both arms of this study a specific high dose chemotherapy module, HDC-19, will (if available in patient´s mother tongue) be used as a complement to the QLQ-C30. Assessments will be made after inclusion in the study when the patient´s clinical status is deemed stable, *and* at 12 and 24 months after inclusion. QoL instrument will be collected form non-relapsed patients, and sent to the NSO. Statistical methods will be used as outlined in Sprangers et al (2002) giving guidelines for interpretation of QoL changes over time.

Safety Assessments

Days in hospital
The number of days when the patient stayed over-night for medical reasons will be recorded in both study groups during the first year after inclusion. This is to be able to roughly estimate and compare patient´s strain, safety and utilization of medical resources.

Adverse Event (AE) Reporting
Control groups: Patients treated for AML with chemotherapy will inevitably experience several well recognized adverse events, such as neutropenic fever. For the purpose of this study, such AEs need not to be reported. However, unexpected *and* clinically significant symptoms (as per the investigators judgement) occurring during the first year after patient´s inclusion, should be reported. Terms and severity should be provided according to CTCAE (Appendix VII).

RICT groups. The severity and distribution of AEs after RIC transplants are imperfectly described in the literature. Focus of AE reporting in this study is on the RICT patients, in which an assessment of treatment-related signs and symptoms will be made. The adverse events reported on the CRF will include
• Acute and chronic GvHD, se Appendix V.
• Infections, such as CMV or deep fungal infection..
• Liver toxicity.
• Need for treatment on intensive care unit.
• Organ failure such as renal insuffiency.
• Engraftment syndrome (idiopathic pneumonia syndrome).
• Other organ damage or failure.
• Post-transplantation lymphoma or other malignancies.
• Other significant events, such as severe or unexpected infection or treatment-related toxicity.
• Terms and severity should be provided according to CTCAE, Appendix VII).

Serious Adverse Event (SAE) Reporting
Criteria for seriousness of any adverse event include death, life-threatening, hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, and any other medically important event. As is the case for AEs (see above), most patients are expected to experience SAEs, such as hospitalization due to febrile neutropenia or relapse. *For the purpose of this study, serious adverse events that are regarded as expected events considering the given treatment and underlying disease, need not be reported as SAEs*. However, all deaths and unexpected, significant SAEs should be reported. See the paragraphs below in this section for further details.
• If several SAEs occur at the same time, they can be reported together but on separate pages.
• All unexpected SAEs should also be reported to the Ethics Committee according to local regulations.
• Data on number and types of SAEs will be continuously updated and made available for the Safety Monitoring Board.

To report or not report SAEs

Death

Throughout the entire study period, all deaths should be reported to the national study office (NSO) as SAEs within 3 working days. From the NSO, SAE reports should be forwarded to the CSO without delay.

Life Threatening Adverse Event

- *Do not report* the following types of life-threatening events:
  - events which are expected complications of AML treatment, including anemia, febrile neutropenia, trombocytopenia with or without bleeding.
  - events related to relapse, ie symptoms or signs which prove to be caused by recurrent AML disease.
- *Report* **t**he following types of life-threatening events:
  - unexpected life-threatening events, (as per the investigator´s judgement).
  - events leading to treatment on intensive care unit, or organ failure such as renal insuffiency with dialysis, or other organ damage or failure

In-Patient Hospitalization or Prolongation of Hospitalization

- *Do not report the* following types of events:

- hospitalizations related to expected complications of AML treatment, including anemia, febrile neutropenia, trombocytopenia with or without bleeding
- hospitalizations related to relapse, ie symptoms or signs which proves to be caused by recurrent AML disease
- hospitalizations for scheduled AML treatment.

• *Report* within three working days **t**he following types of events:

- unexpected hospitalizations, as per the investigator´s judgement.
- hospitalizations leading to treatment on intensive care unit with or without ventilator, or organ failure such as renal insuffiency with dialysis, or other organ damage or failure

Persistent or Significant Disability/Incapacity

All SAEs in this category should be reported.

Important Medical Event

These may not result in death or be life threatening or require hospitalization, but they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasms requiring treatment in the ER or home or convulsions that do not result in inpatient hospitalization.

• *Do not report* the following type of events:

- Events representing a relapse or an expected change or progression of the baseline malignant disease.

• *Report* within three working days the following type of events:

- Events, which as per the investigator´s judgement are important, clinically significant and unexpected , including new malignancies.

Summary of SAE Reporting

• All deaths should be reported within 3 working days to the national study office.
• All other SAEs should *in principle* be reported to the NSO within three working days; however serious adverse events that are expected considering the given treatment and underlying disease need not be reported as SAEs.

Follow-Up

All study related or serious adverse events should be followed until they are resolved, become chronic or stable. Resolution of such events should be documented on the appropriate CRF.

Safety Monitoring Board

A Safety Monitoring Board including two from the study independent persons, will perform the safety analysis. The board members are Professor Hans Wadenvik MD, PhD Sahlgrenska University Hospital, SE-413 45, Göteborg, Sweden) and Dr. Jeannine Kassis, MD, FRCPC, Montreal, Canada. Data on number and types of Serious Adverse Events will be updated and made available for the Safety Monitoring Board every 6 months.

Study termination, stopping rules

Regular study termination. All patients will be followed for a minimum of two years after inclusion. The study will be terminated when the last included surviving patient has been followed for two years.
Premature study termination. An analysis of non-relapse mortality (NRM) will be performed in the RICT groups after 20 transplant procedures. If the NRM at 200 days is =40% (8/20 patients) the Study Steering Committee and the Safety Monitoring Board (see below) will consider termination of the study. This analysis was performed and presented at the EBMT meeting 2010.

A new safety analysis will be performed when the follow-up is =12 months for the first 20 patients in the MUD/RICT group. If NRM at that time is >30% the Study Steering Committee and the Safety Monitoring Board (see below) will consider terminating the study.

11. STATISTICAL CONSIDERATIONS

The primary analyses will be performed on the intent-to-treat (ITT) populations with treatment allocation as described in Section 7, see also Flow chart (Appendix XI). The stochastic component of the potential MSD RICT/Control assignment procedure comes from the chance that a sibling is HLA-identical. The corresponding stochastic component of the MUD RICT/Control assignment procedure emanates from the chance of finding a MUD within a reasonable time (as judged by the investigator). To avoid bias, it is essential that any donor search has not been initiated at the time of registration.

As described in Section 7, the formal inclusion point for a registered patient in the study is when a blood sample for tissue typing of the first potential sibling donor is obtained or the patient´s CR1 date if it is later, or – for patients without potential sibling donor - when a request for a MUD search is dispatched, *or* the CR1 date if the patient is registered for the study prior to CR1.

Study Population and Baseline Comparability
The following clinical and demographic characteristics will be tabulated and compared between the treatment arms: age, sex, performance status at inclusion, time from diagnosis to inclusion,time from CR to inclusion, WHO AML diagnosis, French-American-British (FAB) class, secondary AML, karyotype (original reports) later to be classified as high- or intermediate-risk categories,WBC at diagnosis, antecedent disease treated with chemotherapy or radiotherapy, number of induction courses to reach CR, marrow blast percentage after the first induction course. Baseline medical history and physical examination findings will also be tabulated.

Statistical Analyses
The *primary objective* is to compare overall survival from the inclusion point between MSD/RICT and Control treatment for patients with a potential MSD. This is done by combining two strata: Box 1 vs. Box 2 in the flow chart for patients where a MUD search is not an option, and Box 3 vs. Box 5 where a MUD search is planned if a MSD is not found. In the latter stratum “Late failures” before MUD search starts will be included in the control group with weights equal to the proportion of patients in Box 5 relative to the total number of patients in Box 4 and Box 5. According to the argument in the next paragraph patients who turn non-eligible for transplantation during the MUD search are allocated to MUD/Control (Box 5). Patients lost to follow-up or patients refusing further participation in the study, will be censored the date they were last known to be alive. Log-rank tests and Cox regression models will be used for analyses and Kaplan-Meier curves will be used for illustration. Disease-free survival will be analyzed parallel to overall survival.

A *secondary objective* is to compare survival and disease-free survival for MUD/RICT and MUD/Control. This is done by combining two strata: Box 6 vs. Box 7 in patients with a primary MUD search and Box 4 vs. Box 5 in patients with a secondary MUD search. Patients who turn non-eligible for transplantation (e.g. due to relapse or toxicity) during the MUD search before a MUD is found constitute a group that is difficult to handle in a statistically correct way, since MUD search then will be stopped before the MUD search period has ended. This will most probably occur late in the period when there is a relatively small chance left to find a MUD for the patient. Hence, in the main analyses these patients will be allocated to the MUD/Control group, provided non-eligibility occurs before the identification and medical approval of a MUD. Patients with an identified and approved MUD will be allocated to the MUD/RICT group.

Another secondary *objective* is to compare any donor/RICT vs. Control, and this is ascertained by combining the results for MSD and MUD.

Non-relapse mortality and relapse incidence will be analyzed taking competing risks into account, e.g. using the cumulative incidence function.

Biological allocation, as in the present study, is not equivalent to strict randomization. For instance, it is more likely to find an HLA-compatible sibling if the patient has many siblings. Moreover, age might affect a sibling´s suitability as donor. Such factors may in turn be related to a patient´s prognosis

(e.g. via social factors), and thus they are potential confounders that might introduce bias in the treatment comparison. For this reason the survival analyses will also be performed adjusted for known potential confounding and prognostic factors.

The main analyses, outlined above, are intended to mirror ITT analyses for truly randomized trials. Then the *intention* to use a certain treatment is evaluated, albeit both groups (RICT and Control) will be diluted by patients who receive other treatments than those planned. As a complement, Per Protocol (as treated) analyses will also be performed. The time from inclusion to transplantation may be relatively long and hence the analyses will be adjusted for time to transplant using a time dependent transplant indicator in the Cox analyses. All events before transplantation will then be assigned to the Control group. These analyses may potentially yield better power than the "ITT" analyses, but bias may be introduced with advantage for transplantation if late transplantations generally are performed on patients with relatively better prognosis.

Landmark analyses analyses will also be done comparing survival from the landmark for patients who are and who are not transplanted at this time. The landmark will be chosen so that 90% of all transplants have been done.

Since treatment policies vary, subgroup analyses will be performed by country. Adverse events and Quality of Life data will be presented in descriptive tables. All hypothesis tests, and construction of confidence intervals, where appropriate, will be performed using two-sided tests at the 0.05 significance level and 95% confidence level, respectively.

Dimensioning of the Study

The sample size calculation is based on the planned analysis of the primary endpoint, overall survival in the MSD/RICT versus Control comparison. The basic hypothesis rests on an assumption of an overall survival three years after inclusion of 30 % in the control group and 50 % in the RICT group, and this corresponds to a relative hazard of about 1.75 assuming exponentially distributed survival times. The Control group estimate, 30%, is based on data from the Swedish population-based AML-registry (Billström 2002), whereas the hypothetical outcome in the RICT group is based on presently available data in the literature (see Background). We assume that there will be approximately as many RICT as Control patients. With a univariate Cox regression analysis (asymptotocally equal to the logrank test) and a two-sided significance level of 5%, one gets approximately power 80% with d=100 events (deaths) in the MSD part of the study and power 90% with d=134 events (Piantodosi S, 1997). The number of patients needed depends on the true death rate and the follow-up time. Suppose that 40% of the patients will be dead at the end of of the trial. Then n=d/0.40 patients are needed in the trial; e.g. n=250 if d=100. To detect a relative hazard of 1.50 corresponding to an increase in 3-year survival from 0.30 to 0.45, one needs 192 events to reach 80% power and 256 events to reach 90%. The dimensioning is necessarily based on quite simplified assumptions, and is thus approximate.

12. ADMINISTRATIVE CONSIDERATIONS

Quality Control and Quality Assurance
Study Site Visits. Each investigator is responsible for the conduct of the study at his/her site, including completeness and accuracy of data, adherence to local regulations and ethical guidelines. During the course of the study, a representative of the study management may make site visits to review protocol compliance, compare CRFs and source documents, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Ethics
Ethical Conduct of the Study. The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions, (Appendix I) or by the laws and regulations of the country, whichever provide the greater protection for the individual.
Independent Ethics Committee. It is the responsibility of the investigator to obtain approval of the study protocol/amendments from the IEC. All correspondance with the IEC should be filed by the investigator.

The study will not be started until approval of the protocol, the Patient Information and the Informed Consent Form for patients and donors has been obtained from the appropriate Health authority and Ethics Committee. It is the responsibility of the investigator to keep a copy of the written approval and, where possible, a list of the members, their titles or occupation, and their institutional affiliations. The approval should include a study identification number and the date of review. Protocol amendments are to be submitted to the Ethics Committee (and other local authorities, according to local regulations) prior to implementation.

The investigator will make all required progress reports to the Ethics Committee as well as report serious adverse events, life-threatening problems or deaths as required by local regulations. The Ethics Committee must be informed at the termination of the study.

Patient Information and Consent
It is the responsibility of the investigator to give each subject prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The subject must be informed about his right to withdraw from the trial at any time. Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and will not prejudice further medical treatment. It is the responsibility of the investigator to obtain signed informed consent from all subjects prior to inclusion in the trial.

Potential Sibling Donor Information and Consent
Siblings to patients considered for inclusion in the study, will be approached and informed of the study. At the initial contact, the sibling will be assessed by a brief history with regard to major contraindications to stem cell donation. If no such contraindications are revealed, the sibling will asked if she/he is willing to undergo HLA-typing. In case of HLA-identity, the sibling will receive detailed oral and written information about G-CSF mobilization and PBSC harvest – and the bone marrow harvest option - and asked for a formal informed consent (Appendix III). Further blood sampling and medical work-up of the sibling donor will take place only after this form has been signed.

Unrelated Donor Information and Consent
Unrelated donor search and work-up will be performed as per established routines.

Case Report Forms (CRF)
There will be a CRF binder for each patient. All CRFs should be completed in English and in a neat, legible manner to ensure adequate interpretation of data. Black ink should be used to ensure clarity of all reproduced CRFs. Any modification of previously entered data should be made by striking through the original entry with a single line, initialing and dating the change, and entering the correct data

nearby. Use of opaque correction fluid, correction tape and highlighters is prohibited. The CRF must be signed by the investigator.

CRFs should be completed without undue delay and forwarded via the NSO to the data management team for data entry. Any comments, corrections or questions will be raised by return fax, telephone, or email directly to the site with instructions for correction procedures or pursuit of incomplete data. The original of the CRF will be retained in the investigator's study files.

Record Retention

The following documents should be kept in the study files:

a. The original protocol and all amendments.
b. Copies of current curricula vitae of the principal investigator and all co-investigators.
c. Copies of all regulatory documents required by local and national regulators.
d. Final IRB/IEC approval, annual renewals, and all IEC correspondence.
e. All patients' signed Informed Consents.
f. The final completed CRF for each patient.
g. All correspondence to/from the study management.
h. A blank Informed Consent Form and a blank CRF.
i. A list of patients enrolled on the study (containing patient initials, study specific patient number, hospital identification number).
j. A Screening Log for all patients approached with reasons why they were not eligible.
k. Site signature form.

The Principal Investigator is responsible for maintaining the study files for at least two years following the publication of the results of this study.

Standard operating procedures (SOPs)

A Study Steering Committee (SSC) with members representing participating countries will govern the study. SSC will decide on amendments of the protocol and has to be continuously updated on the progress of the study and all serious adverse events. There will be a national study office (NSO) in each country who has national operational responsibility, and a central study office (CSO) in Göteborg, Sweden. The details of document traffic, data handling and validating, site audit and monitoring will be described in separate SOPs, produced for the study. In short:

- The NSO provides assistance and expertise with the study and operational issues.
- The ormorm should be faxed to the NSO. The NSO, formally includes patients fulfilling inclusion/exclusion criteria. After inclusion the fax is forwarded to the CSO.
- CRF forms are faxed to the NSO where they are inspected. Whenever requested by the NSO corrections are made by the site and the form faxed again. Eventually, approved forms are forwarded to the CSO.
- SAE forms are faxed to the NSO and should be forwarded to the CSO as soon as their accuracy is confirmed.
- NSO is responsible for the accuracy of data forwarded to the CSO and for monitoring on site if needed.

Publication of Results

All manuscripts for publication or abstracts for presentations must be approved by the Study Steering Committee prior to submission. At the end of the study, the Steering Committee will appoint a Manuscript Preparation Group and oversee the manuscript development. Authorship will be determined by the Steering Committee.

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APPENDIX I, DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975,
35th WMA General Assembly, Venice, Italy, October 1983,
41st WMA General Assembly, Hong Kong, September 1989,
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996,
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

Basic principles for all medical research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. ¸Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

Additional principles for medical research combined with medical care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX II

Information till forskningspersoner om studien:

Klinisk fas III studie av allogen benmärgstransplantation med reducerad konditionering jämfört med standardbehandling för patienter med akut myeloisk leukemi

Inledning

I denna information beskrivs en klinisk undersökning, dvs ett forskningsprojekt. Frågeställningen är om *allogen benmärgstransplantati*on är bättre än cytostatikabehandling för patienter i din situation. Du kommer att få detaljerad muntlig information, men vi ber dig ändå läsa igenom dessa sidor för att lättare kunna ställa frågor och avgöra om du vill delta i studien.

Vem tillfrågas om att delta i studien?

Du blir tillfrågad om du vill delta i studien eftersom du har akut myeloisk leukemi (AML).

Bakgrund

Akut myeloisk leukemi (AML) är en allvarlig blodcancersjukdom som behandlas med cytostatika (”cellgifter”). De första kurerna syftar till att åstadkomma *remission*, dvs man ser ingen leukemi i blod och benmärg. Trots detta finns stor risk för återfall och därefter är chansen till bot liten.

Transplantation av *blodbildande stamceller* från ett syskon eller en obesläktad donator (allogen benmärgstransplantation; BMT) har visats minska risken för återfall i AML, men proceduren har tidigare varit förbehållen yngre patienter. En ny teknik för BMT (*mini-transplantation; RICT*) utnyttjas numera hos äldre patienter.

Återfall av AML innebär små chanser till bot.

Vad är en allogen mini-transplantation (RICT)?

Proceduren innebär att patienten ges en måttligt stark cytostatikabehandling. Därefter ges blodbildande stamceller från en donator (syskon eller obesläktad) till patienten ungefär som vid en blodtransfusion. De nya cellerna från donatorn är aktiva och har möjlighet att utplåna kvarvarande leukemiceller.

Vid en RICT utnyttjas donatorns celler för förhindra återfall.

Hur går det till - och vilken är avsikten med denna studie?

Du kommer att vara en av ungefär 350 patienter – från Sverige, Kanada, Norge, Finland eller Tyskland. Om det finns skäl att gå vidare med en RICT startar sökning efter en donator. Om du inte har syskon som passar kan man leta i stora internationella register. Chansen att finna en lämplig donator är cirka 60%. Utan passande donator kan en BMT inte genomföras.

Patienter med en identifierad donator utgör *Transplantationsgruppen* och för dessa planeras en RICT. Övriga patienter utgör *Kontrollgruppen*.

Vi vet inte om RICT leder till fler botade AML-patienter jämfört med enbart cytostatikabehandling.
Vår avsikt är att besvara denna viktiga fråga.

Risker, obehag och eventuell nytta med deltagande

• Patienter i *Kontrollgruppen* kommer i de flesta fall att få 1-3 ytterligare cytostatikabehandlingar. Dessa behandlingar pågår ett par månader och är förknippade med risker för infektioner och andra komplikationer.

• Patienter i *Transplantationsgruppen* genomgår en RICT. Även här finns risk för infektioner men andra komplikationer kan uppträda. Vid *Graft-versus-Host sjukdom (GvHD)* kan donatorns vita blodkroppar ge upphov till inflammation i flera organ. GvHD kan i vissa fall ge svåra symptom, men uppträder oftast i en mildare form. Alla patienter ges förebyggande behandling mot GvHD men

ytterligare medicinering med kortison kan behövas. Tät kontakt med sjukhuset behövs i flera månader efter en RICT.

BMT innebär risker men vår förhoppning är att risken för återfall ska minska kraftigt.

Studietidens längd.
Du kommer att kontrolleras i åtminstone två år.

Behandlingsalternativ
Om du väljer att inte delta i denna studie kommer du att få fortsatt behandling med cytostatika.

Kostnader
Du kommer inte att få någon ersättning för ditt deltagande i denna studie.

Ersättning för skada
Patientförsäkringen och Läkemedelsförsäkringen gäller för patienter som deltar i denna studie. Det finns ingen ersättning att få därutöver. Du bör kontakta din läkare om du har några frågor eller om du tror att du har fått en skada som har samband med ditt deltagande i denna studie.

Personuppgiftsansvar
Ansvaret för behandlingen av dina personuppgifter har Sahlgrenska Universitetssjukhuset och hanteringen regleras av Personuppgiftslagen (SFS 1998:204). Du kan vända dig till sjukhusets personuppgiftsombud (Johanna Rydbäck, (johanna.rydback@vgregion.se), tel 342 1000) om du önskar utdrag av de personuppgifter som finns registrerade på dig.

Sekretess
Uppgifter om dig och din sjukdom kommer att lagras på vanligt sätt i den elektroniska patientjournalen. Från denna samlas vissa uppgifter in och förs över till särskilda rapportformulär. På dessa formulär syns din identitet bara som ett kodnummer. All personal som arbetar med studien har tystnadsplikt. Det kommer inte att gå att identifiera dig i forskningsrapporter från studien.

Ny kunskap
Du kommer att få reda på ifall det kommer fram något som är av betydelse för din hälsa, ditt välbefinnande eller ditt beslut att delta i denna studie.

Ditt deltagande är frivilligt
Ditt deltagande i denna studie är helt frivilligt. Du kan avböja att delta, och ifall du bestämmer dig för att delta så kan du när som helst avbryta utan att du behöver ange något skäl. Detta kommer inte att påverka vårt bemötande av dig.

Studieledning

Ansvarig läkare:	*Lokalt ansvarig läkare:*	*Nationell koordinator*
Mats Brune, docent, överläkare Sektionen för Hematologi Sahlgrenska Universitetssjukhuset 413 45 Göteborg tel 031 342 7349		Inger Andersson. Leg ssk. FD Sektionen för Hematologi Sahlgrenska Universitetssjukhuset 413 45 Göteborg tel 031 342 6823

Underskrift

Min underskrift här nedanför betyder att jag väljer att delta i denna studie.

- Jag har fått muntlig information om studien och jag har läst den skriftliga informationen här ovanför. Jag har haft möjlighet att ställa frågor.
- Jag är medveten om att mitt deltagande i denna studie är frivilligt, och att jag kan avbryta mitt deltagande när som helst utan att ange något skäl.
- Om jag väljer att inte delta i studien kommer bemötandet av mig inte att försämras, och min fortsatta behandling kommer att ges som planerat.
- Min underskrift här nedanför innebär att jag samtycker till datainmatning och bearbetning av uppgifter från mitt deltagande. Det kommer att vara omöjligt att identifiera mig som deltagare i studien i kommande rapporter av resultaten.
- Jag samtycker också till att blod och benmärg som tas i samband med denna studie får sparas för att bekräfta resultaten.
- Jag får behålla en kopia av denna undertecknade information.

_____ _____

Patientens underskrift Datum

_____

Namnförtydligande

_____ _____

Informationen given av (namn, telefon) Datum

APPENDIX III

Information till syskondonatorer om studien:

Klinisk fas III studie av allogen benmärgstransplantation med reducerad konditionering jämfört med standardbehandling för patienter med akut myeloisk leukemi

Syfte
Din syster eller bror behandlas för akut myeloisk leukemi (AML) och deltar i en klinisk studie, dvs ett forskningsprojekt. Din medverkan behövs för att ditt syskon ska kunna genomgå en benmärgstransplantation. I denna information tillfrågas du om ditt samtycke till att donera blodbildande stamceller – antingen direkt från benmärgen eller insamlade från blodet. Syftet med studien är undersöka om benmärgstransplantation ökar andelen botade patienter jämfört med enbart cellgifter.

Bakgrund
Blodbildande stamceller finns i benmärgen där de ger upphov till alla typer av blodkroppar. Överföring av sådana stamceller *från* ett syskon *till* en patient kallas allogen benmärgstransplantation och kan vara ett livräddande ingrepp vid leukemi. Vid en sådan transplantation används oftast stamceller som samlats in från givarens blod. Efter undersökning av din och ditt syskons vävnadstyp har vi funnit att du är lämplig som donator av stamceller.

Genomförande
Steg 1 består av läkarundersökning och kontroll av blodprover, till exempel HIV-test, för att utesluta smittsamma sjukdomar eller andra åkommor som förhindrar din fortsatta medverkan.
Steg 2 innebär insamling av blodstamceller som sen ges till ditt syskon. Se nedan

Insamling av blodstamceller eller benmärg, risker och obehag
Det finns två sätt att samla in blodbildande stamceller för transplantation. Efter den detaljerade information du kommer att få av transplantationsläkaren kan du själv ange önskemål om vilken procedur du föredrar.

1. Insamling av blodstamceller är en rutinmässig procedur. Under fyra dagar ges injektioner under huden med G-CSF (Neupogen®). Substansen får stamceller att lämna benmärgen och svämma ut i blodet där de är lätt åtkomliga. Ett vanligt obehag vid Neupogen-behandling är smärtor i skelettet. Dessa besvär behandlas med milda smärtstillande medel, tex Alvedon. Under själva stamcellsinsamlingen förkommer lätta obehag som behandlas med tillförsel av kalk. Allvarliga biverkningar är oerhört sällsynta
2. Man kan också samla in stamceller direkt från benmärgen. Detta görs i narkos på operationsavdelningen. Benmärg dras ur bäckenet genom upprepade punktioner. Vanliga besvär efterår är stelhet, småvärk och tillfälligt lågt blodvärde.

Frivillighet
Din medverkan i denna studie är frivillig.
• Du kan avböja eller avbryta deltagande utan att ange något skäl.
• Du kan också ange en orsak för att avböja eller avbryta deltagande utan att denna orsak förs in i din journal eller på annat sätt meddelas till någon annan, inklusive ditt syskon.
• Om du är tveksam och överväger att avbryta ditt deltagande bör detta meddelas ansvarig läkare så snart som möjligt och i varje fall minst en vecka före utsatt transplantationsdatum.

SAMTYCKE

• Jag har läst ovanstående information. Jag har också fått muntlig information och haft möjlighet att ställa frågor. Min underskrift här nedanför betyder att jag väljer att delta som donator i denna studie.

• Jag samtycker till att genomgå läkarundersökning, och att donera stamceller på något av de sätt som beskrivits för mig.

• Jag har läst stycket ”Frivillighet” ovan och vet att min medverkan är frivillig, och jag kan återkalla detta samtycke utan negativa följder för mig från sjukvårdens sida.

• Jag samtycker till datainmatning och bearbetning av uppgifter från mitt deltagande i denna studie för forskningsändamål. Det måste vara omöjligt att identifiera mig som deltagare i studien i kommande rapporter av resultaten.

• Jag samtycker också till att blod och stamceller som tas i samband med denna studie får frysas, sparas och eventuellt användas till mitt syskon i senare skeden. Cellerna får inte användas till något annat ändamål.

_____ _____

Underskrift Datum

_____

Namnförtydligande

_____ _____

Informationen given av (namn, telefon) Datum

APPENDIX IV

Time plan for evaluations

The Table is an overview showing when CRFs sections should be faxed to the study office.

CRF sections #		**Reporting points**[1]	**Important data**
All patients			
Registration Form		**Before or after CR1**	Dates of donor search. Intention to MUD?
Control group	**RICT group**		
1	1	Inclusion	Quality of Life #1
2	**2**	+ 6 months	Treatment assignment Chimerism, acute GvHD Early complications
3	**3**	+ 12 months	Quality of Life #2. Days in hospital during the first year Chronic GvhD
4	**4**	+24 months	Quality of Life #3
5	**5**	+36 months	Chronic GvhD
6	**6**	+48 months	Chronic GvhD
7	**7**	+ 60 months	Chronic GvhD
10	**10**	Death and some SAEs Pts´ discontinuation	**Patient Discontinuation Form**, should be filled out at pt´s *death* (within 3 days), or *lost to follow-up* or *withdrawn consent.*
20	**20**	Relapse	**Relapse form.** After relapse, data are retrieved on this form (and #10) only.
30	**30**	At study termination	**Study Termination Form**, for reports at study termination.
40	**40**	Within 3 days after certain SAEs.	**Serious Adverse Event Form** to be used in case of serious and unexpected SAEs

[1]Reporting points are from date of Inclusion.

APPENDIX V

Graft-versus-Host Disease

Acute GvHD (aGvHD)

• If patient develops aGVHD at any time after allo-SCT, aGVHD is graded as outlined below.

Clinical Stage of aGvHD according to organ system

Stage	Skin	Liver	Intestine
1	maculopapular rash <25% of body surface	Bilirubin 2-3mg/dl (34-50 μmol/L)	500-1000ml diarrhoea/day or nausea/vomiting with biopsy confirmative of upper GI GvHD
2	maculopapular rash 25-50% of body surface	Bilirubin 3-6mg/dl (51-102 μmol/L)	>1000-1500ml diarrhoea/day
3	maculopapular rash >50% of body surface area or generalised erythroderma	bilirubin 6-15mg/dl (103-255 μmol/L)	>1500ml diarrhoea
4	generalised erythroderma with bullous formation and desquamation	Bilirubin 15mg/dl (>255 μmol/L)	>1500ml diarrhoea/day plus severe abdominal pain with or without ileus

Overall Clinical Grading of Severity of Acute GVHD

Grade	Skin	Liver	Intestine
I	1-2	0	0
II	0 1-3 1-3 3	1 *and/or* 0-1 1 0	1 1 0-1 0
III	0-3 0-3 0-3	2-3 0-3 4	0-2 2-3 0-3
IV	0-3 4	0-4 0-4	4 0-4

Chronic GvHD (cGvHD)

If patient develops cGVHD at any time after allo-SCT, cGVHD is graded traditionally as outlined below. If a patient dies before D +100 and has not developed cGVHD, the patient is not evaluable for cGVHD.

Limited chronic GVHD

Either or both

- localised skin involvement
- hepatic dysfunction due to chronic GVHD

Extensive chronic GVHD

Either

- generalised skin involvement, or
- localised skin involvement and/or hepatic dysfunction

and at least one of

- liver histology showing chronic aggressive hepatitis, or
- involvement of eye (Schirmer's test with <5mm wetting), or
- involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy, or
- involvement of any other target organ

In addition chronic GvHD will be described using NIH Criteria (Filipovich et al. Biol Blood Marrow Transplant. 2005: 11;945-955). See case report forms.

APPENDIX VI.

Common Terminology Criteria for Adverse Events

Could be used and/or downloaded at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

APPENDIX VII

ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, Confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

APPENDIX VIII

WHO Histological Evaluation of AML

Can be found at

http://www.cancer.gov/cancertopics/pdq/treatment/adultAML/healthprofessional/page2

APPENDIX IX

EORTC Quality of Life Instrument (QLQ-C30; version 3

Vi är intresserade av några saker som har med Dig och Din hälsa att göra. Besvara alla frågor genom att sätta en ring runt den siffra som stämmer bäst in på Dig. Det finns inga svar som är "rätt" eller "fel". Den information Du lämnar kommer att hållas strikt konfidentiell.

Var vänlig fyll i Dina initialer: _____
När är Du född? (Dag, Månad, År): _____
Dagens datum (Dag, Månad, År): _____

		Inte alls	**Lite**	**En hel del**	**Mycket**
1.	Har Du svårt att göra ansträngande saker, som att bära en tung kasse eller väska?	1	2	3	4
2.	Har Du svårt att ta en lång promenad?	1	2	3	4
3.	Har Du svårt att ta en kort promenad utomhus?	1	2	3	4
4.	Måste Du sitta eller ligga på dagarna?	1	2	3	4
5.	Behöver Du hjälp med att äta, klä Dig, tvätta Dig eller gå på toaletten?	1	2	3	4

Under veckan som gått:		**Inte alls**	**Lite**	**En hel del**	**Mycket**
6.	Har Du varit begränsad i Dina möjligheter att utföra antingen Ditt förvärvsarbete eller andra dagliga aktiviteter?	1	2	3	4
7.	Har Du varit begränsad i Dina möjligheter att utöva Dina hobbys eller andra fritidssysselsättningar?	1	2	3	4
8.	Har Du blivit andfådd?	1	2	3	4
9.	Har Du haft ont?	1	2	3	4
10.	Har Du behövt vila?	1	2	3	4
11.	Har Du haft svårt att sova?	1	2	3	4
12.	Har Du känt Dig svag?	1	2	3	4
13.	Har Du haft dålig aptit?	1	2	3	4
14.	Har Du känt Dig illamående?	1	2	3	4
15.	Har Du kräkts?	1	2	3	4
16.	Har Du varit förstoppad?	1	2	3	4

Under veckan som gått:		**Inte alls**	**Lite**	**En hel del**	**Mycket**
17.	Har Du haft diarré?	1	2	3	4
18.	Har Du varit trött?	1	2	3	4

19.	Har Dina dagliga aktiviteter påverkats av smärta?	1	2	3	4
20.	Har Du haft svårt att koncentrera Dig, t.ex. läsa tidningen eller se på TV?	1	2	3	4
21.	Har Du känt Dig spänd?	1	2	3	4
22.	Har Du oroat Dig?	1	2	3	4
23.	Har Du känt Dig irriterad?	1	2	3	4
24.	Har Du känt Dig nedstämd?	1	2	3	4
25.	Har Du haft svårt att komma ihåg saker?	1	2	3	4
26.	Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Ditt familjeliv?	1	2	3	4
27.	Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Dina sociala aktiviteter?	1	2	3	4
28.	Har Ditt fysiska tillstånd eller den medicinska behandlingen gjort att Du fått ekonomiska svårigheter?	1	2	3	4

Sätt en ring runt den siffra mellan 1 och 7 som stämmer bäst in på Dig för följande frågor:

29. Hur skulle Du vilja beskriva Din hälsa totalt sett under den vecka som gått?

1	2	3	4	5	6	7
Mycket dålig						Utmärkt

30. Hur skulle Du vilja beskriva Din totala livskvalitet under den vecka som gått?

1	2	3	4	5	6	7
Mycket dålig						Utmärkt

En del patienter upplever att de har några av följande symtom eller problem. Var vänlig och ange i vilken grad som du besvärats av dessa symtom eller problem under den senaste veckan. Sätt en ring runt den siffra som best beskriver ditt tillstånd. I formuläret används cancer som ett samlingsnamn för samtliga elakartade blodsjukdomar (leukemi, myelom, myelodysplastiskt syndrom etc).

Under den sista veckan	**Inte alls**	**Lite**	**En hel del**	**Mycket**
31. Har Du känt Dig frusen?	1	2	3	4
32. Har Du känt dig yr?	1	2	3	4
33. Har Du haft ökad slemproduktion i mun och svalg?	1	2	3	4
34. Har Du haft sår i munnen?	1	2	3	4
35. Har Du besvärats av muntorrhet?	1	2	3	4
36. Har Du besvärats av smakförändringar?	1	2	3	4

37. Har Du haft klåda på huden?	1	2	3	4
38. Har Du besvärats av torr hud?	1	2	3	4
39. Har Du besvärats av stelhet i leder?	1	2	3	4
40. Har Du haft muskel- eller skelettvärk?	1	2	3	4
41. Har Du varit orolig för att få återfall av Din cancersjukdom?	1	2	3	4
42. Har Du varit orolig för att få någon annan form av cancer?	1	2	3	4
43. Har Du varit orolig för Din hälsa med tanke på framtiden?	1	2	3	4
44. Har Du haft någon att prata med om Din oro?	1	2	3	4
45. Har Du varit orolig för att Du kan komma att bli steril?	1	2	3	4
46. Besvaras endast av män: Har Du haft några problem med potensen?	1	2	3	4

	Inte alls	Lite	En hel del	Mycket
47. I vilken grad har Du varit intresserad av sex?	1	2	3	4
48. I vilken grad har Du varit sexuellt aktiv?	1	2	3	4

Besvara endast nästa fråga om du varit sexuellt aktiv!

49. Till vilken grad har Du känt sexuell tillfredställelse?	1	2	3	4

REGISTRATION FORM (FROM SITE NUMBER……..)

Hospital…….. Investigator:…… Fax: ……

Patient Initials: ___ ___ ___ Date of Birth: ____/____/____ Date AML Dx: ___/___ /____
yy mm dd *yy mm dd*

(See Page 2 for comments)	(check box) Yes	No	Comments
1. AML with good risk features			
2. Planned to receive myeloablative conditioning			
3. Able to tolerate RICT and consolidation chemotherapy			
4. Signed informed consent			Date:
5. Attained CR1?			
6. If pt has at least one potential sibling donor			
6a. HLA typing of any sibling performed?			
6b. Search for a MUD planned if sibs unfit or not HLA-id?			
7. *If pt has no potential sibling donor*			
Search for a MUD planned?			

…….…… …….…… ……
Date Signature (investigator) Printed name

Send to National Study Office (Göteborg) by fax 031 82 57 36 or email (inger.em.andersson@vgregion.se)

9. REGISTRATION CONFIRMATION

	Yes	No	Date, comment
Patient registered for the study			

Assigned UPN: ……

…….…… …….…… ……
Date Signature Printed name

Comments on the
Registration Form

Introduction. The *registration form* is a document confirming that the investigator and her/his patient have agreed to aim for a reduced intensity conditioning transplant (RICT) performed in accordance with Amendment #2 of the TRALG-01 study, applying the routines for donor search and donor selection outlined in the protocol. The Registration Form must not be sent after any donor search has been initiated.

The paragraphs below refer to page 1 of the Form.

1. Pts with known good risk features should not be registered. However, if some information is pending, eg cytogenetics, patients could be registered. Write "Not yet known" under Comments.

2. Pts should not be planned for a full dose conditioning.

3. Pts should be fit for RICT or consolidation chemotherapy.

4. Written informed consent should be obtained before registration.

5. In order to shorten the time between diagnosis and transplant, *registration* of pts for the study is permitted and encouraged before or after attained CR1 - but in each case prior to any donor search. For patients registered after attained CR1, formal *inclusion* time point is defined as the date of HLA typing of the first potential sibling donor, *or* for pts without a potential sib, the date of sending a search request to a donor registry. For patients registered before attained CR1, formal *inclusion* time point is defined as the date of CR1.

The date of CR1 will be retrieved in the CRF Part 1. Registered patients who eventually do not attain CR1 will not be formally included in the study, but followed for survival.

6. Patients with a potential sibling donor. A "potential sibling donor" is a sibling willing to undergo HLA-typing, and who has no apparent contraindication to PBSC or BM harvest.

6a. The registration form should be sent not later than the date of blood sampling of the first potential sibling donor.

6b. The *intention* <u>to</u> – or <u>not to</u> – proceed with a MUD search in case the potential sibling donor(s) are not eligible should be recorded here. If the clinical situation is uncertain, the caring physician may decide to delay sending the registration form until the situation has resolved.

7. ***Patients without a potential sibling donor*.** The registration should be sent not later than the date of initiation (ie dispatching a search warrant) of a MUD search. This date, as well as the date of CR1 will be retrieved in the CRF Part 1.

8. *Registration confirmation*. The National PI (or designee) checks the registration form and thereafter (i) confirms patient registration; (ii) assigns each registered patient a Unique Patient Number; (iii) sends back the form to the investigator.