Clinical Study Protocol

Study Title:

A prospective, multicenter European Registry for newly diagnosed patients with Myelodysplastic Syndromes of IPSS low and intermediate-1 subtypes.

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2

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Signatures

Study Title:

A prospective, multicenter European Registry for newly diagnosed patients with Myelodysplastic Syndromes of IPSS low and intermediate-1 subtypes.

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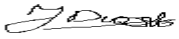
Dr Jackie Droste	Study Co-ordinator		18th December 2007

Protocol Synopsis

Study Title:

A prospective, multicenter European Registry for newly diagnosed patients with Myelodysplastic Syndromes of IPSS low and intermediate-1 subtypes.

Study Objectives:

To describe the demographics and the disease-management of IPSS low and intermediate-1 MDS patients who are newly diagnosed and classified according to the WHO criteria.

To collect and to present data on clinical characteristics, disease-management and relevant outcomes.

Methodology:

Data on patients with low or intermediate-1 risk MDS will be collected prospectively at diagnosis and at 6-months intervals after diagnosis. The data will be gathered by eleven existing national MDS Registries that are represented within the LeukemiaNet MDS Working Party and will be combined in one central European Database. Data analyses will be conducted by the Data Management Centre after every 400 patients included in the European Registry and at the end of the follow-up period.

Number of Patients & Centres

Eleven hematology centres in eleven different countries (Austria, Czech Republic, France, Germany, Greece, Italy, Netherlands, Rumania, Spain, Sweden and United Kingdom) will participate in this Registry. The recruitment target is a minimum of 1000 and a maximum of 2000 cases.

Population:

The study population will consist of newly diagnosed patients with IPSS low- or intermediate-1 risk myelodysplastic syndrome.

Study Duration:

The enrollment time will be 18 months. The follow-up period will be 5 years.

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List of abbreviations

AML	Acute Myeloid Leukemia
BM	Bone Marrow
CI	Confidence Interval
CRF	Case Report/Record Form
ECG	Electrocardiogramm
EQ-5D	EuroQol 5D
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IPSS	International Prognostic Scoring System
LDH	Lactate Dehydrogenase
LIC	Liver Iron Content
LVEF	Left Ventricular Ejection Fraction
MCV	Mean Corpuscular Volume
MDS	Myelodysplastic Syndromes
QOL	Quality Of Life
RA	Refractory Anemia
RARS	Refractory Anemia with Ringed Sideroblasts
RAEB-1	Refractory Anemia with Excess of Blasts 1
RAEB-2	Refractory Anemia with Excess of Blasts 2
RBC	Red Blood Cells
RCMD	Refractory Cytopenia with Multilineage Dysplasia
RCMD-RS	Refractory Cytopenia with Multilineage Dysplasia and Ringed Sideroblasts
TLP	Time to Leukemia Progression

WBC	White Blood Cells
WHO	World Health Organization

1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematopoietic stem cell disorders. They are characterized by dysplasia in the myeloid, megakaryocytic and/or erythroid lineages. The abnormal cells belong to a malignant clone, which represses the remaining normal cells in the bone marrow. Patients suffer from peripheral blood cytopenias (anemia, leukopenia and/or thrombocytopenia). The natural course of MDS ranges from an indolent disease that may span years, to a more acute manifestation with severe bone marrow failure resulting in life-threatening complications. About 30% of the patients show progression towards acute myeloid leukemia (AML), but most patients eventually die from complications of bone marrow failure.

1.1 Incidence of MDS

The overall incidence of MDS is estimated to be 3-4 per 100 000 per year. Approximately 70% patients will be defined as low-risk disease. These numbers are often based on local studies. It is generally assumed that the incidence is underestimated due to the complexity of diagnosing MDS. The more indolent forms of MDS, when the number of blasts in the bone marrow or blood is not or only slightly increased, are especially difficult to diagnose. In clinical practice today, cytomorphologic evaluation of the peripheral blood and bone marrow still is the basis of MDS diagnostics. The clonal hematopoietic cells show dysplastic features. However, there are a number of other conditions, such as infections or medication that can result in transient cytopenias and dysplastic cells, without clonal aberrations. In approximately 50% of patients chromosomal abnormalities are found using conventional cytogenetics, which can facilitate the diagnosis of MDS.

1.2 Classification of MDS

Classification systems have been developed to serve as a guide for the diagnosis, estimation of prognosis and management of patients with this disease. However, newly acquired knowledge about the pathogenesis of MDS and the development of novel forms of therapy require that classification systems are continuously open to changes.

The World Health Organization has provided a system that classifies patients according to the number of cell lineages affected, the number of blasts in peripheral blood and bone marrow, the presence of ringed sideroblasts and the result of cytogenetic analysis. Patients with RA (-RS), RCMD (-RS), or a solitary deletion of the long arm of chromosome 5, have a relatively good prognosis regarding survival and risk of developing acute myeloid leukemia. Prognosis is worse in the RAEB-1 subgroup. Patients with RAEB-2 in general have the highest risk of progression to AML and the lowest overall survival.

The International Prognostic Scoring System (IPSS) was recently developed for assessment of prognosis. The IPSS system comprises three parameters, bone marrow blast percentage, karyotype and number of cytopenias. Patients with a low or intermediate-1 score are more likely to have an indolent disease course (often defined as “low-risk). Patients in the intermediate-2 or high risk group are more likely to suffer from aggressive disease with a higher frequency of transformation to acute myeloid leukemia.

1.3 Treatment of MDS

As MDS is a heterogeneous disease, so is its treatment. Management decisions are partly based on the WHO classification and IPSS score. Allogeneic stem cell transplantation remains the only potentially curative treatment. Due to the lack of suitable donors, the intensity of this treatment and the fact that most patients are over the age of 60, stem cell transplantation is only available to a limited number of patients. The care of patients with MDS has improved during the past decades. For example, the implementation of growth factors and immunomodulating agents has improved the management of patients with IPSS low and intermediate-1 risk MDS. Also, drugs are being developed to prevent and to treat the complications of MDS, such as infections or transfusion-induced iron overload. A number of new drugs are under investigation. Although cooperation between centres has led to the development of national and international guidelines on the treatment of MDS, there is a large variation in clinical management. Published data on the management of MDS are mainly based on local experience.

1.4 MDS Registry

The current registry is designed to collect information about a large cohort of newly diagnosed MDS patients with low-risk disease defined as IPSS low or intermediate-1 categories. In a number of countries, MDS Registration projects are ongoing. These registries aim at improving the knowledge of the local incidence and management of these patients. Ìn this project, data will be collected using registries in several European countries as the platform for registration. This will create an international registry to study the demographics and disease-management of patients with MDS.

2. Study objectives

2.1 Primary objective

The primary objective of this study is to describe the demographics and the disease-management of newly diagnosed MDS patients within IPSS low and intermediate-1 categories.

2.2 Secondary objectives

The secondary objectives are:

1. To investigate any correlation between:
   - Clinical characteristics (including WHO classification and known prognostic factors) at inclusion
   - Secondary iron overload due to transfusions
   - Treatments received

   and

   - Overall survival (censored at 5 years)
   - Time to Leukemia Progression (TLP)
   - Performance status (appendix 3), EQ-5D (appendix 4)

2. To collect safety data on treatment with iron chelators, when applicable, including:
   - Renal safety (serum creatinine, creatinine clearance and urine protein)
   - Liver safety (serum liver transaminases)

3. Investigational Plan

3.1 Overall Study Design

The registry is designed to collect information about a large cohort of newly diagnosed MDS patients. Patients will be prospectively assessed in the context of existing registries[1] represented within the LeukemiaNet MDS Work Package. Patients will be observed until death, or for a maximum of 60 months.

- Enrollment: each centre should register all consecutive eligible patients who present during the enrolment period of 18 months from the starting date of the study, or until the achievement of the study recruitment target. Patients with IPSS low or intermediate-1 MDS can be included up to 3 months after diagnosis.
- Follow-up: follow-up visits will be scheduled according to the standard practice of the centre and to the treating physician's best judgment. Clinical data will be collected if available. It is assumed that at least an assessment every six months (in the context of regular follow up visits) will be performed. Laboratory evaluations for disease or iron chelation treatment monitoring may be performed more often; values available at follow up visits will be recorded.

In this study, no clinical, instrumental or laboratory assessments will be performed other than those required for disease management according to local best practice, or required to monitor iron chelation treatment as per the approved Summary of Product characteristics. The only exceptions will be the Patient Reported Outcomes (PRO) questionnaires and blood (and urine) sample collection for biological correlative studies. In selected countries and centers, ancillary quality of life, cardiac function and pharmacoeconomics sub-projects will be launched to collect information about the quality of life of patients and costs implications of the therapeutic strategies (separate protocols).

3.2 Study Population

3.2.1 IPSS risk group

The European Registry will be limited to patients with low or intermediate-1 risk MDS. These represent a group that is generally considered to have a more indolent disease course. Most patients with IPSS low or intermediate-1 risk receive supportive or non-intensive treatment. The main aims of the treatment are to reduce morbidity and mortality and to provide an acceptable quality of life. Management of anemia includes administration of red cell transfusions and iron chelation therapy to prevent or to treat transfusion-induced hemosiderosis. Also, treatment with growth factors, immunomodulators, demethylating agents or immunosuppression can increase hemoglobin levels in a subset of patients. Prevention of the complications of thrombocytopenia is important, as is the prevention and treatment of infections with antibiotics. A number of drugs that may improve the care for these patients are under investigation.

[1] Austria, Czech Republic, France, Germany, Greece, Italy, Netherlands, Romania, Spain, Sweden, United Kingdom

3.2.2 Size of Study Population

A minimum of 1000 and maximum of 2000 patients will be enrolled in this study. The aim is to yield approximately 500 to 1000 subjects at the end of 5 years of observation. All patients will have been diagnosed with myelodysplastic syndrome within 3 months of enrolment. This sample size is intended to be a broad representation of the European MDS patients and sufficiently large for meaningful analysis of MDS subgroups.

3.2.3 Inclusion Criteria

Patients must meet all of the following criteria to be included in the European MDS Registry:

- Male or female.
- Age ≥ 18 years.
- Newly diagnosed patient (within 3 months from the date of the diagnostic bone marrow aspirate).
- MDS classified according to WHO criteria (2001).
- IPSS Risk group Low or Intermediate-1[1].
- Able and willing to provide the written informed consent.

3.2.4 Exclusion Criteria

- Age <18 years
- Patient unwilling or unable to give consent
- intermediate-2 or high risk MDS
- secondary/therapy-related MDS.

3.2.5 Withdrawal from the Study

Patients will be withdrawn from the study in case of:

- Progression to leukemia.
- Necessity to treat the patient with intensive chemotherapy.
- Treatment with a drug that changes the natural history of the disease or prevents follow-up.
- Withdrawal of consent without a reason required

In any of these cases, only data on survival will be collected.

[1] the cytogenetic profile is strongly recommended for the diagnosis. However if impossible to be performed, the patient can be included in the study providing that the percentage of blasts in the bone marrow is less than 5% **and** the cytopenia score = 0 (0/1 cytopenia).

3.3 Visits and Assessments

3.3.1 Visit Schedule and Assessments

3.3.1.1 At inclusion

The following data will be collected at inclusion of the patient:

- Inclusion and Exclusion Criteria.
- Date of patient inclusion.
- Demographic information: sex, date of birth, ethnicity.
- Weight, height.
- Karnofsky Performance Status (appendix 3), EQ-5D (appendix 4).
- History of MDS: date of MDS diagnosis, WHO classification, IPSS risk group.
- Treatment for MDS :
  - therapies for MDS.
  - red cell transfusion: date of first transfusion, number of transfusions in the prior year, date of last transfusion and number of units transfused, pre-transfusion hemoglobin value.
  - if treatment with iron chelator is given: dose and schedule, start and stop date, and ferritin value with date if available.
- Concomitant diseases, including but not limited to cardiac insufficiency, ophthalmic conditions including lens opacities and cataract, hearing impairment, diabetes mellitus, endocrine dysfunctions, renal or liver disease.
- All concomitant medication.
- Laboratory values:
  Peripheral blood: hemoglobin concentration, White cell count, neutrophil, lymphocyte, monocyte, eosinophil and basophil count, platelet count, MCV, reticulocytes, glucose, LDH, liver transaminases, ferritin, erythropoietin, transferrin saturation level, serum creatinine and calculated creatinine clearance
  Bone marrow: date of bone marrow aspirate and/or biopsy, percentage of blasts, percentage of ring sideroblasts, cytogenetics (karyotype).
  Urine: urinalysis for protein (by dipstick).
- Blood and urine samples for biological correlative studies

3.3.1.2 At each follow up visit (every 6 months), including end of study:

- Date of visit.
- Weight
- Karnofsky performance status (appendix 3), EQ-5D (appendix 4)
- Changes in concomitant conditions and medication since last visit.
- Number of transfusions since last visit, date of last transfusion and number of units, pre-transfusion Hb

- If treatment with iron chelators was started: dose and schedule, start date and pre-treatment and ferritin.
- Laboratory values:
  Peripheral blood: hemoglobin concentration, White cell count, neutrophil, lymphocyte, monocyte, eosinophil and basophil count, platelet count, MCV, reticulocytes, glucose, LDH, liver transaminases, ferritin, erythropoietin, transferrin saturation level, serum creatinine and calculated creatinine clearance
  Bone marrow: date of bone marrow aspirate and/or biopsy, percentage of blasts, percentage of ring sideroblasts, cytogenetics (karyotype).
- *Urine:* urinalysis for protein (by dipstick).
- Patient outcome:
  - in case of MDS progression to a more advanced WHO subtype / AML: provide the date of progression.
  - in case of death: provide date and cause of death.
- Blood and urine samples for biological correlative studies

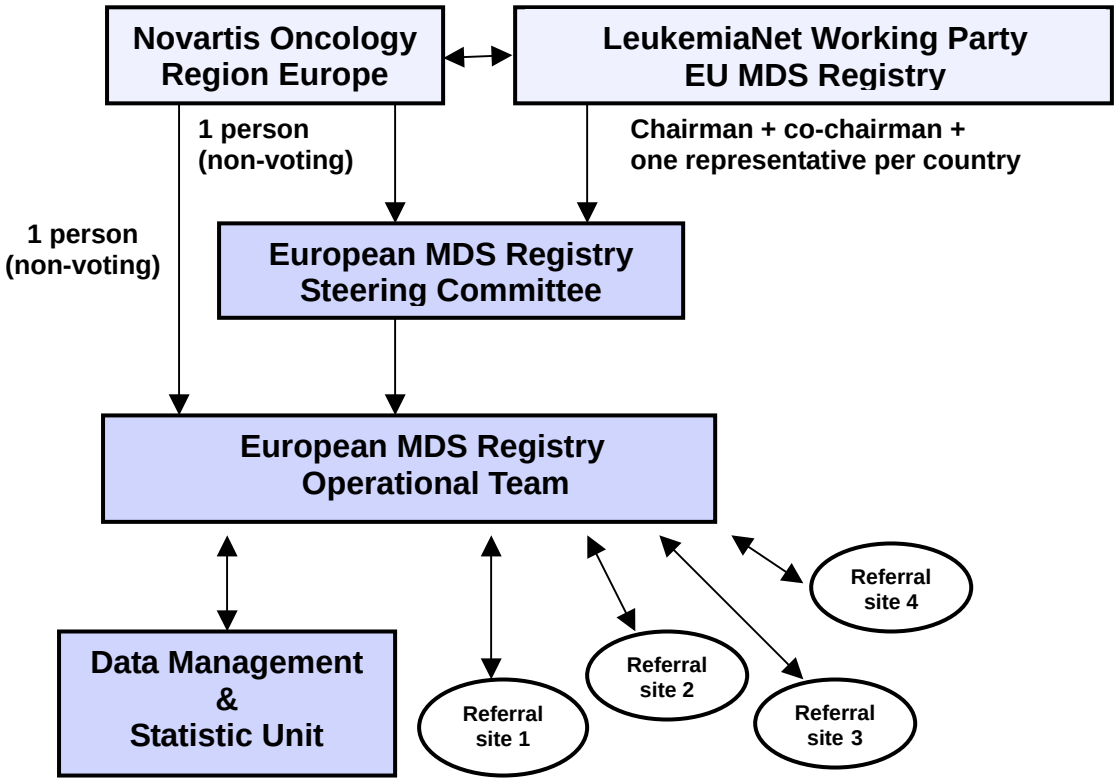
3.3.2 Laboratory Tests

Laboratory tests will be performed as judged appropriate by the treating physician. This study does not require additional laboratory tests to be performed. The laboratory test results of interest will be registered if available.

4. Organisation and Responsibilities

4.1 Overall organization

The European MDS Registry is an initiative of the LeukemiaNet MDS Work Package and was set up in cooperation with Novartis Oncology. The steering committee of the project consists of representatives of both parties. The registry will be built using data collected by several centres (referral sites) in the context of their local registries. The collection of data will be coordinated by the operational team, which consists of representatives from all parties involved. There is a central organization responsible for the management of data and a central unit involved in the statistical analysis.



4.2 Steering committee

The steering committee will consist of representatives from all participating countries, the project manager (non-voting member) and a representative from Novartis Oncology (non-voting member).

The steering committee is responsible for the study protocol. The steering committee selects the sites for participation in the registry and monitors the availability of resources at all sites. A feasibility study will be conducted in order to estimate the number of patients to be expected per year. There will be monitoring of the patient inclusion rate during the enrolment period of the study. The statistical analysis plan has to be approved by the steering committee. Finally the steering committee takes decisions concerning publication policy and authorship.

During the inclusion period, the steering committee will meet every 3 months by telephone conference and every 6 months in a plenary session. During the follow-up phase of the study, meetings will take place at least once a year in a plenary session. The secretary of the steering committee will be responsible for drafting the minutes of each meeting and circulating this document after approval.

4.3 Operational Team

The operational team will be chaired by the project manager from the sponsor institution. It will consist of the data managers and/or research nurses from the referral sites, representatives from the Central Data Management and Statistic Unit, an administrator for the regulatory issues and archive and one representative from Novartis Oncology (non-voting member).

The operational team is responsible for the overall coordination of the project. This includes the arrangement of support for the contract duties, the distribution of sites metrics, such as the number of patients included, coordination of the referral sites and the organisation of Site Training. Also, the operational team will organize all meetings and will prepare and distribute the agenda and minutes. Finally, the operational team will support the preparation of publications.

During the inclusion period, the operational team will meet every month by telephone conference and every 6 months in a plenary session. After completion of recruitment, the team will meet at least every 6 months in a plenary session. The project manager is responsible for the preparation of the minutes of each meeting and circulation of this document. Also, it is the duty of the project manager to report the important issues to the members of the steering committee.

4.4 Central Data Management and Statistic Center

The Central Data Management and Statistics center is responsible for the design and maintenance of the core database. The data management center will prepare working instructions related to the data entry and cleaning, will execute the data cleaning and will provide a database lock. The statistics center will prepare and execute the statistical analysis. It will provide statistical support during the preparation of publications and will provide metrics by site.

5. Statistics

The Central Statistical Unit is responsible for the development of the details of the statistical analysis plan. The detailed statistical analysis plan has to be approved by the Steering Committee. This also applies whenever changes in the analysis plan are being considered.

5.1 Sample size

This study is exploratory in nature. Thus, the estimated sample size is not based on a statistical hypothesis, but on an estimation of the number of patients who are diagnosed with MDS per center in an 18 months period and sufficiently large to inform some subgroup analyses.

5.2 Collection of clinical variables

All data collected for each patient will be displayed in the patient data listings. Unless otherwise stated, *baseline* is defined as the first observation at the time the patient is included in the European Registry. The tabulation of laboratory data, vital signs and LVEF will indicate the normal ranges for each variable. Each value will be classified as falling above, below or within normal limit. It is impossible to use a single central laboratory for all parameters and all patients. However, to avoid the issue of collecting hundreds of normal ranges, standard normal ranges will be defined and applied for the purpose of statistical analysis.

5.3 Demographics and disease management

A descriptive analysis will be performed at each cut-off and at the end of the follow up period. Any changes from the values at inclusion of the patients will be recorded and analyzed. This will include:

- The proportion (with 95% CI) of patients that progress to leukemia. The median, range and 95% CI for time to leukemia progression. Kaplan-Meier curves will be used for this analysis. Time to leukemia progression is defined as the time from diagnosis to the date of the first objective progression to leukemia or the last date the patient was assessed and found to be progression-free. Patients who are lost to follow-up or die of any cause (including non disease-related deaths) without documentation of progression will be censored at the last date they were assessed and found to be progression-free. Patients who have not progressed or died will be censored at the last date they were found to be progression-free.

- The proportion (with 95% CI) of patients that die during follow-up. The median, range and 95% CI for survival. Overall survival (censored at 5 years) will be analyzed using Kaplan-Meier curves. Overall survival is calculated for all patients from the date of MDS diagnosis to the date of death from any cause. Patients with no documented death will be censored at the last date they were known to be alive. Patients who are alive after five years of follow-up will be censored. Patients who received therapy known to modify the natural history of MDS will be censored on day 1 of this treatment.

- The proportion (with 95% CI) of patients that experiences iron overload, cardiac failure, renal failure and/or other co-morbidities.

- The median, range and 95% CI for time to development of iron overload defined as ferritin > 1000 ng/l on two measurements at least one month apart (in the absence of an alternative cause of raised ferritin). Time to the initiation of treatment aimed at prevention or reduction of iron overload.

- The proportion (with 95% CI) of patients treated with iron chelators (including type, dose and schedule of treatment).

5.4 Correlation between patient characteristics and prognosis

A multivariate Cox proportional hazards regression model will be applied to correlate survival with several patient characteristics. These include clinical variables, such as the WHO classification at enrolment, but also the development of secondary iron overload due to transfusions and the treatments received during the course of the disease.

A similar exploratory analysis will be applied to investigate the relationship between these patient characteristics and time to leukemia progression, development of co-morbidities (concerning cardiac and renal function) and patient reported outcomes (including EQ-5D and QOL assessments)

5.5 Interim analysis

Intermediate descriptive analyses will be conducted after every 400 patients included in the European Registry. The first interim analysis will allow an accurate determination of the characteristics of the study population (mainly demography, characteristics of the MDS disease and its history and treatments, concomitant diseases and relevant treatments) and any center effect for recruitment. Once 800 patients have completed at least 2 years of follow up, descriptive data will allow a more accurate statistical analytical plan to be developed defining sample size to adequately power important secondary endpoints.

6. Data recording and data management

6.1 Data recording

Data will be recorded and entered through the web-based e-CRF at each national registry site and at clinical sites within each country. A screening log will be maintained at each site to ensure consecutive patient enrolment. There will be a dedicated resource (nurse, data manager or equivalent) for each national registry site. This resource will be an employee of the Referral Site. He or she will co-ordinate data entry with the clinical sites and will be responsible for validation of data from all clinical sites prior to upload ito the central study Database. All data collected for each patient will be displayed in the patient data listings. History and clinical conditions are assessed from routine documentation and clinical evaluation performed in the context of inclusion and follow up visits. The data management centre will be responsible for generation of queries.

6.2 Data Management

The Data Management Center is responsible for the import of data from the national registry sites and for the merging of all data in a central database. Procedures concerning data export, cleaning and database merging will be described in the Data Management Manual. Training will be provided for each site and a helpdesk will be available.

7. Quality Control and Quality Assurance

The European Registry is a non-interventional study. Therefore, it is not considered necessary to conduct close monitoring activities with 100% source data verification for all patients. Instead, the quality of the data provided by the referral sites will be evaluated on a sample of patients. This evaluation will be conducted by a monitor independent from the clinical sites. The monitor will report the results directly to the Sponsor.

In order to ensure source data verification, the participating centers must provide access to all relevant clinical records. Information concerning the identity of the patient will not leave the center.

8. Ethics and GCP Compliance

8.1 Subject identification and protection

Patients will be cared for according to their treating physician's best judgement. They will not be subjected to any experimental treatment or examination for the purposes of this study. The only exceptions will be the EQ-5D questionnaires and 6-monthly blood/urine sampling for biological correlative studies. Patient identifiers will not be recorded in the Registry. An identification number will be allocated to each patient registered, including a code to indicate which local registry registered them.

The protocol will be reviewed by the Local, Regional or National Ethics Committees.

8.2 Informed Consent

All patients who are eligible for inclusion will be informed of the aims and nature of the study. They will be informed of the fact that all clinical data concerning them will be treated confidentially, but that their medical records may be reviewed by authorized persons other than their treating physician for study purposes.

All patients will be informed that participation is voluntary and that the patient is allowed to refuse participation at any time, without consequences for his or her further treatment. Documented informed consent must be obtained for all patients before they are registered. The informed consent procedure must conform to the ICH guidelines on Good Clinical Practice and must be in accordance with national and local regulatory requirements.

9. Financing and Insurance

The project is an investigator initiated study from the European LeukemiaNet. The study sponsor is the University of Nijmegen and the study is funded by Novartis Oncology Europe.

10. Publication Policy

Data and analyses will remain property of the European LeukemiaNet. Novartis Oncology will have the right to use report data. The publication policy will be defined by the Steering Committee.

11. References

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A. Appendices

A.1 WHO classification of myelodysplastic syndromes

Type MDS	Peripheral blood	Bone marrow
Refractory anaemia (RA)	Anaemia No or rare blasts	Erythroid dysplasia only <5% blasts <15% ringed sideroblasts
Refractory anaemia with ringed sideroblasts (RARS)	Anaemia No blasts	Erythroid dysplasia only <5% blasts ≥15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods <1x10^9/L monocytes	Dysplasia in ≥10% of the cells of two or more myeloid cell lines <5% blasts in marrow No Auer rods <15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods <1x10^9/L monocytes	Dysplasia in ≥10% of the cells in two or more myeloid cell lines ≥15% ringed sideroblasts <5% blasts No Auer rods
Refractory anaemia with excess blasts -1 (RAEB-1)	Cytopenias <5% blasts No Auer rods <1x10^9/L monocytes	Unilineage or multilineage dysplasia 5-9% blasts No Auer rods
Refractory anaemia with excess blasts -2 (RAEB-2)	Cytopenias 5-19% blasts Auer rods ± <1x10^9/L monocytes	Unilineage or multilineage dysplasia 10%-19% blasts Auer rods ±
Myelodysplastic syndrome - unclassified (MDS-U)	Cytopenias No or rare blasts No Auer rods	Unilineage dysplasia: one myeloid cell line <5% blasts No Auer Rods
MDS associated with isolated del(5q)	Anaemia Usually normal or increased platelet count <5% blasts	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts Isolated del(5q) No Auer rods

A.2 International Prognostic Scoring System

Prognostic Variable	Score Value				
	0	**0.5**	**1.0**	**1.5**	**2.0**
BM blasts (%)	<5	5-10		11-20	21-30
Karyotype*	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

* Good risk: normal, -Y, del(5q), del(20q)
Poor risk: complex (≥ 3 abnormalities) or chromosome 7 anomalies
Intermediate risk: other abnormalities.

Scores for risk groups are as follows:

Low, 0; Intermediate-1, 0.5-1.0; Intermediate-2, 1.5-2.0; and High, ≥ 2.5

A.3 Karnofsky Performance Status

The Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

A.4 EQ-5D

Figure 1: EQ-5D (UK English version)
By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
I have no problems in walking about □
I have some problems in walking about □
I am confined to bed □□

Self-Care
I have no problems with self-care □
I have some problems washing or dressing myself □
I am unable to wash or dress myself □

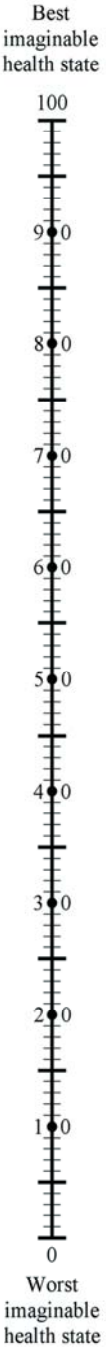
Usual Activities (*e.g. work, study, housework, family or leisure activities)*
I have no problems with performing my usual activities □
I have some problems with performing my usual activities □
I am unable to perform my usual activities □□

Pain/Discomfort
I have no pain or discomfort □
I have moderate pain or discomfort □
I have extreme pain or discomfort □

Anxiety/Depression
I am not anxious or depressed □
I am moderately anxious or depressed □
I am extremely anxious or depressed □

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.
We would like you to indicate on this scale how good or bad your own health is today, in your opinion.
Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own Health state today



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A.5 Protocol for blood and urine sample collection and processing

Serum

- The anticoagulant used for serum should be plain clot activator tubes (silica activator only)
  (These Tubes are typically red top (serum) when sourced from Greiner and Becton Dickinson for example)

- Please do not use tubes containing gel or separators
- Please collect the blood directly into the tubes, not via a syringe

1. Collect 20 mls of blood into a plain tube(s) containing silica activator. Record time of sample collection on the sample record form.
2. Serum should be allowed to clot for 1 hour before centrifugation. Centrifuge the samples for 10 minutes, 20°C, 2,000g (approximately 3,000 rpm in many bench top centrifuges – needs to be checked as varies with centrifuge type and size). Any deviations from these times should be recorded on the sample record form.
3. Following centrifugation of the serum tube(s), remove as much of the serum as possible without disturbing the red cells using a fine point Pastette and place into a pooling tube (bijoux). Once serum collection is complete for a sample, use a second Pastette and divide the serum equally between 4 pre-labeled screw top or Eppendorf storage tubes. Write the patient trial ID number and sample date on the tubes using a permanent marker pen.
4. Store the sample tubes at -70°C/-80°C. Record the time of freezing and any deviations from the above protocol.

Urine

1. Collect 5 mls of urine into a sterile universal container
2. Centrifuge the samples for 10 minutes, 20°C, 2,000g (approximately 3,000 rpm in many bench top centrifuges – needs to be checked as varies with centrifuge type and size). Any deviations from these times should be recorded on the sample record form.
3. Using a sterile Pastette carefully remove urine to 2 pre-labelled screw top or Eppendorf storage tubes leaving approximately 1 ml and any pelleted debris to be discarded. Write the patient trial ID number and sample date on the tubes using a permanent marker pen.
4. Store the sample tubes at -70°C/-80°C. Record the time of freezing and any deviations from the above protocol.

IF SAMPLES ARE TO BE SENT FOR PROCESSING TO A REGIONAL LABORATORY THEY *MUST* BE PROCESSED ON THE DAY OF COLLECTION. THE TIME OF COLLECTION AND TIME OF CENTRIFUGATION MUST BE RECORDED ON THE SAMPLE COLLECTION FORM.

ALL STORED SAMPLES WILL BE SENT FROZEN IN BATCHES TO LEEDS.

Enquiries contact
David Buchanan, Senior Research Nurse, Leeds Teaching Hospitals +44 113 392 2879
David Bowen, Consultant Haematologist, Leeds Teaching Hospitals +44 113 392 5153

A.6 Sample collection record for ELN MDS Registry

Sample Record Form ELN MDS Registry

Please complete in block capitals and using a black ball point pen

Patient ID (study no.)…….. Clinical centre …….

Visit number……..

Date of Sample (DD/MM/YY) ☐☐/☐☐/☐☐

	24hr (hh/mm)			
Time of venepuncture				
Time of freezing – SERUM samples				
Time of urine sample collection				
Time of freezing – URINE samples				

Number of tubes frozen

Serum ☐

Urine ☐

Blood tubes used for venepuncture

Becton Dickinson ☐

Greiner ☐

Sarstedt ☐

Other (please specify) _____

Comments (please document any deviations from the protocol, for example sample processing delays, missing parts of samples, haemolysis etc)

_____
_____

When this form has been completed please:

- Fax a copy to Leeds (F.A.O Deborah Sherratt , FAX no. +44 113 392 6244)
- Keep the original safely in the site file