Protocol Synopsis

Study Title:

A prospective, multicentre European Registry for newly diagnosed patients with Myelodysplastic Syndromes (MDS), including Acute Myeloid Leukaemia (AML) with 20-≤30 percent marrow blasts (former RAEB-t), and Chronic Myelomonocytic Leukaemia (CMML).

Short Title:

European MDS Registry

Study Objectives:

To collect and to describe the demographics, disease-management, and treatment outcomes of MDS[1] patients who are newly diagnosed and classified according to the WHO criteria[2].

To perform observational studies concerning relevant scientific research questions in MDS using clinical data and biological samples, and to present relevant research outcomes in the fields of diagnosis and prognostication, health related quality of life issues, health economics, and risk stratification for newly developed classes of drugs.

To disseminate the results of the studies to all stakeholders involved, including patients, health care givers, health care authorities, health insurance companies, pharmaceutical companies and health care professionals.

Methodology:

Data on patients with MDS will be collected prospectively at diagnosis and at 6-month intervals after diagnosis for all registered patients. The data will be collected by twenty-one (or more) countries 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 at the University of York in various sub studies, at specific time points as decided or requested by the SC, but at least once a year included in the European Registry and at the end of the follow-up period.

Number of Patients & Centres

Over 150 haematology centres in twenty-one (or more) different countries (Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, the Netherlands, Poland, Portugal, Republic of Serbia, Romania, Slovenia, Spain, Sweden, Switzerland and United Kingdom) will participate in this Registry. The recruitment target is a minimum of 3000 lower-risk MDS and 1000 higher-risk cases.

Population:

The study population will consist of newly diagnosed patients with all subtypes of MDS classified according to the WHO criteria[2], including therapy-related MDS and MDS-F, AML with 20-≤30 percent marrow blasts (former RAEB-t), and CMML and other forms of mixed MDS/MPD.

Study Duration:

The enrolment time will continue at least until December 31st 2025 but extension of the recruitment period is possible. The follow-up period will be until termination of the EUMDS Registry (up to 17.5 years after enrolment or longer if the study is extended).

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[1] The abbreviation of MDS will cover all subgroups described in the study population, if not mentioned otherwise.

[2] Both the WHO-2008 and WHO-2016 classification will be recorded.

1. Introduction

Myelodysplastic syndromes (MDS)[2] are a heterogeneous group of haematopoietic stem cell disorders.[1] They are characterized by dysplasia in the myeloid, megakaryocytic and/or erythroid lineages. The abnormal cells belong to a (pre-)malignant clone, which usually represses progressively the remaining normal cells in the bone marrow. Patients with MDS suffer from peripheral blood cytopenias (anaemia, 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 leukaemia (AML), but most patients eventually die from complications of bone marrow failure.

Incidence and diagnosis:

The overall incidence of MDS is estimated to be 3-4 per 100,000 per year, but the incidence increases to 32.1%/100.000 per year among those aged 80 years.[2] The incidence is generally underestimated due to the complexity of diagnosing MDS, which accounts especially for the more indolent forms in elderly patients. In the last decades the incidence of MDS seems to have increased. In part this may be due to an increased readiness to perform bone marrow examinations in the increasing population of elderly persons. Furthermore, treatment with radiotherapy and / or certain chemotherapeutic agents promotes the development of therapy-related MDS and AML (tMDS/tAML).[3] Approximately 70% of the patients can be defined as low-risk (IPSS-R low & very low risk and intermediate risk) and 30% as high-risk disease (IPSS-R high & very high risk).[4]

According to the WHO classification and most published guidelines, the diagnostic procedure encompasses morphology, histopathology, and a cytogenetic analysis. Flow cytometry and next-generation sequencing may also aid the diagnostic process, both for MDS and especially CMML.[5, 6] The MDS-RIGHT project recently published European guidelines for management of MDS (https://mds-europe.eu/management.

Classification:

The World Health Organization (WHO) [7] 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 AML. 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. One of the major changes in the WHO classification compared to the earlier FAB (French-American-British) classification [8, 9] was lowering of the blast percentage for a diagnosis of AML from 30% to 20%. As a consequence refractory anaemia with excess blasts in transformation (RAEB-t) was eliminated from the MDS classification and included in the AML diagnosis.[7]

Chronic myelomonocytic leukaemia (CMML) was eliminated from the MDS category because of features at the time of initial presentation of both a myelodysplastic disease as well as a myeloproliferative disease (MDS/MPD). The WHO-2001 criteria classified CMML into two prognostic subclasses, CMML-1 and CMML-2, based on the number of blast cells in the blood and bone marrow.[7] In 2008, the WHO classification was updated with several minor changes in comparison to the 2001 WHO classification scheme.[10] The WHO-2016 criteria, have minor changes in comparison to the WHO-2008.[11, 12]

The initial International Prognostic Scoring System (IPSS) from 1997 was revised in 2012.[4, 13] Patients were subdivided in 5 prognostic groups based on an improved cytogenetic risk calculation, and more detailed subdivision of the cytopenias and percentage of marrow blasts. The IPSS-R has proven its value as a more refined risk stratification tool in our lower risk MDS registry by identifying a group of patients with a high/very high IPSS-R risk score (5%) within the IPSS low and intermediate-1 groups.[14] The EUMDS Registry has analysed the value of IPSS-R in the first 1,000 patients entered in the Registry. IPSS-R appeared to estimate prognosis more accurately especially in the intermediate-1 risk patients.[14] In the

near future, it is expected that genetic markers will be increasingly incorporated in the classification of MDS.[15]

Treatment:

Management decisions in MDS are partly based on the WHO classification and IPSS-R score [16] and are described in detail in the updated European Guidelines published on MDS-Europe.eu. Allogeneic haematopoietic cell transplantation (SCT) remains the only potentially curative treatment. SCT is recommended to patients with advanced disease stages. The age at which MDS patients can tolerate a SCT has increased due to modified regimens but SCT above the age of 75 years is still relatively uncommon.

Hypomethylating agents (HMAs) [17-22] are first-line treatment for higher-risk MDS since more than 10 years and they have proven to prolong survival compared to other regimens. In Europe, Dacogen is indicated for the treatment of adult patients with newly diagnosed de novo or secondary AML, according to the WHO classification, who are not candidates for standard induction chemotherapy. Many attempts have been tried to add to the efficacy by combining HMAs with other antineoplastic drugs, but so far, no prospective randomized trial have led to new therapeutic recommendations. A recent combination tested for both AML and MDS is azacytidine plus venetoclax, a bcl2 inhibitor, but firm data are still pending. Intensive anti-leukemic (anti-AML) chemotherapy in the treatment of higher risk MDS patients has not been proven as effective as in de novo AML due to a lower complete remission (CR) rate and remission duration.[23]

Good supportive care remains a central aspect in the management of MDS patients with good prognosis or patients with poor prognosis who are not eligible for stem cell transplantation. Growth factors, including erythropoietin stimulating agents (ESAs) [24], and lenalidomide (for del5q) [25] has improved the management of patients with IPSS low and intermediate-1 risk MDS. Recently, luspatercept has been proven effective in reducing the severity of anaemia in patients with lower-risk MDS with ring sideroblasts who had been receiving regular red-cell transfusions and who had disease that was refractory to or unlikely to respond to erythropoiesis-stimulating agents.[26] In addition, drugs have been developed to prevent and to treat the complications of MDS, such as infections or transfusion-induced iron overload. Although collaboration 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.[17] Published data on the management of MDS were mainly based on local experience and expert opinions.[17, 27] Recently, the European LeukemiaNet guidelines [17] for diagnosis and treatment of primary myelodysplastic syndromes in adults have been updated and redesigned into interactive evidence-based online guidelines (https://mds-europe.eu/management).

European MDS Registry (EUMDS):

The European MDS Registry (EUMDS) started as an observational pan-European study aiming to prospectively collect longitudinal data from a large number of lower-risk myelodysplastic syndromes (MDS) patients in April 2008. In August 2016, the extension to a General EUMDS Registry, including higher-risk (IPSS intermediate-2 and high-risk), therapy-related MDS and MDS-F, AML with 20-<30 percent marrow blasts (former RAEB-t), CMML and other forms of mixed MDS/MPD was approved. The registry has evolved into a valuable source containing data on diagnostics, demographics, clinical parameters, health-related quality of life (HRQoL), disease-management and outcome of over 3000 newly diagnosed MDS patients across more than 150 centres in 21 countries. In a number of these countries, national MDS Registration projects are ongoing aiming at improving the knowledge of the local incidence and management of these patients. The EUMDS registry serves as a central international registry, using the national MDS Registries that are represented within the European LeukemiaNet MDS Working Party (ELN-WP8) as the platform for registration, to study the demographics, disease-management and treatment outcomes in patients with newly diagnosed MDS more comprehensively. The EUMDS Registry has already resulted in numerous publications and presentations at international conferences with regard to the demographics, diagnosis and prognosis, pathogenic mechanisms, patient-reported outcomes (PRO), impact of treatment and health related quality of life in (lower-risk) MDS (see also: https://eumds.org/publications).[14, 28-36]

The aim is to increase the number of patients and follow-up, and to perform scientific studies with the data to improve our knowledge of the course of MDS or related diseases, and to gain insight into the treatment and the outcomes of treatment. This will be used to improve diagnosis and treatment of patients with MDS or related diseases in the future.

2. Study objectives

Primary objective

To collect and to describe demographics, clinical and lab manifestations, epidemiological data, genetic characteristics, HRQoL, disease-management, and treatment outcomes of MDS patients who are newly diagnosed and classified according to the WHO-2008 and WHO-2016 criteria [10, 12], including therapy-related MDS and MDS-F, AML with 20-<30 percent marrow blasts (former RAEB-t), CMML and other forms of mixed MDS/MPD.

Treatment outcomes are defined as: efficacy (including survival, CR, PR and haematological responses as defined in the revised Cheson criteria [37], safety, HRQoL, and Health Economics (see also: secondary objectives).

Secondary objectives

1. To investigate the relationship between:
   - Clinical characteristics (including WHO classification, genetic characteristics, and known prognostic factors) at inclusion and during follow-up
   - Treatments received, including transfusions,

   and
   - Responses to treatment as defined in the treatment section
   - Overall survival (censored at end of follow-up)
   - Time to progression to high risk MDS and to leukaemia
   - Karnofsky Performance Status, general and disease specific HRQoL
   - Health Economics
   - Disease related complications
2. To derive and validate new prognostic scoring systems based on the data obtained
3. To perform observational studies concerning relevant scientific research questions in MDS using clinical data and biological samples and to present relevant research outcomes in the fields of diagnosis & prognostication, HRQoL issues, health economics, risk stratification for newly developed classes of drugs.
4. To disseminate the results of the studies to all stakeholders involved.

3. Study Design

The registry is designed to collect information about a large cohort of newly diagnosed MDS patients from clinical centres within the participating European countries. Patients will be observed until death or until termination of the EUMDS Registry (up to 17.5 years after enrolment or longer if the study is extended).

- *Enrolment:* each centre should register all consecutive eligible patients who present during the enrolment period, or until the achievement of the study recruitment target. Patients can be included up to 100 days 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. Reports of the follow-up visits will be collected every six months. Clinical and laboratory evaluations for disease or treatment monitoring may be performed more often in dedicated studies running in the centres, but the EUMDS Registry will only collect data at 6 months intervals.

In this study, no clinical, instrumental, laboratory assessments, or therapeutic intervention will be performed other than those required for disease management according to local best practice. The only exceptions will be the Patient Reported Outcomes (PRO) questionnaires and blood sample collection for biological correlative studies, including molecular data. In selected countries and centres, ancillary HRQoL, cardiac function and pharmaco-economics sub-projects will be launched to collect information about the HRQoL of patients and cost implications of the therapeutic strategies (separate protocols).

Study Population

The European Registry will be limited to patients diagnosed with MDS, including therapy-related MDS and MDS-Fibrosis, patients with acute myeloid leukaemia (AML) with 20-<30 percent marrow blasts (former RAEB-t), chronic myelomonocytic leukaemia patients (CMML) and other forms of mixed MDS/MPD. The abbreviation of MDS will cover all subgroups described in the study population, if not mentioned otherwise.

Study sample size

The recruitment target is a minimum of 3000 lower-risk MDS and 1000 higher-risk cases. All patients will have been diagnosed with MDS within 100 days 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.

Inclusion Criteria

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

- Age ≥ 18 years
- Newly diagnosed patient (within 100 days from the date of the diagnostic BM aspirate)
- MDS classified according to current WHO criteria (both 2008 [10] and 2016 [12] will be recorded)[3]
    - All sub groups of MDS
    - Therapy-related MDS
    - MDS with Fibrosis (MDS-F)
    - AML with 20-<30 percent marrow blasts (former RAEB-t)
    - CMML and other forms of mixed MDS/MPD
- IPSS and IPSS-R Risk group classification *(mandatory)*[3]
- Able and willing to provide the written informed consent

Exclusion Criteria

- Age <18 years
- Patient unwilling or unable to give consent
- AML with ≥30 percent marrow blasts according to WHO
- Patients with inv(16), t(15;17) and t(8;21) are considered AML and therefore not eligible
- Patients with higher risk MDS progressed from a previously diagnosed lower risk MDS that was not registered within 100 days after first diagnosis of (lower risk) MDS

[3] Cytogenetic data form the basis of MDS risk stratification and proper state of the art treatment of MDS-patients. As of February 2nd, 2015 cytogenetic assessment is mandatory for inclusion in the EUMDS Registry.

Follow-up & withdrawal from the Study

Patients will be followed until termination of follow-up (i.e. death, withdrawal, loss to follow-up, or termination of follow-up period). Patients will be withdrawn from the study in case of:

- Withdrawal of consent. A patient may withdraw consent at any time, without providing a reason.

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

4. Visits and Assessments

The following data will be collected:

At inclusion

- Inclusion and Exclusion Criteria
- Date of patient inclusion
- Demographic information: sex, date of birth
- Weight, height
- Karnofsky Performance Score, EQ-5D and Visual Analogue Score, MDS specific HRQoL (e.g. QUALMS-1*, to be implemented based on availability of language*)
- History of MDS: date of MDS diagnosis, WHO-2008 and 2016 classification, IPSS and IPSS-R risk groups
- If secondary MDS: prior disease and type of treatment or prior and type of exposure to cytotoxics or radiation therapy
- Treatment for MDS:
  - Therapies for MDS:
    - if haematopoietic stem cell transplantation: date of transplantation; graft type and source donor cells/type of donor; response after transplantation: CR (yes/no), date of CR, date of relapse.
    - if (intensive) chemotherapy: start and stop date and type of chemotherapy (schedule), number of cycles; response: CR (yes/no), date of CR, date of relapse.
    - if use of hypomethylating agents (HMA): start date and type of agent; number of cycles, date of last HMA dose; response, according to revised Cheson criteria [37], date end of response according to Cheson revised criteria and/or physician.
    - Other therapies, including haematopoietic growth factors: start date and type of therapy; date of last dose; response, according to revised Cheson criteria [37], date end of response according to Cheson revised criteria and/or physician and date of first post-ESA transfusion due to MDS (excluding operations etc).
  - Best supportive care (BSC, also when concomitant to other 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 during the follow-up interval, pre-transfusion haemoglobin (Hb) value of last transfusion before visit, serum erythropoietin value with date if available.
    - if treatment with iron chelator is given: dose and schedule, start and stop date and type of therapy, duration, reason for discontinuation, ferritin values 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: Hb concentration, white cell count, neutrophil, lymphocyte, monocyte, eosinophil and basophil count, platelet count, MCV, CRP, reticulocytes, glucose, albumin, LDH, liver transaminases, ferritin, erythropoietin, transferrin saturation level, serum creatinine and calculated creatinine clearance
  - Bone marrow: date of BM aspirate and/or biopsy, percentage of blasts, percentage of ring sideroblasts, cytogenetics (karyotype)[4]
  - Urine: urinalysis for protein (by dipstick)
- Samples for biological correlative studies, including molecular studies:

  *For all **new included** patients*
  - 2 x EDTA-blood tubes (each 7 ml) for molecular analyses ***at screening***.
    - *If EDTA-blood is not feasible:* BM aspirate 3-5 ml, or Isolated DNA 2-5 µg of ***screening visit*** (preferred) or at least collected within +/- 3 months before or after diagnosis. Only in the cases that 'patients are not treated' or 'patients are only treated with EPO', samples within +/- 6 months before or after diagnosis.

    Samples will be labelled only with EUMDS ID and date and time of sampling. *Collected samples for molecular analyses will be stored in the central tissue bank of the EUMDS Registry or can be stored in a local or in a national biobank if available.*
  - ***Optional:*** Extra serum sampling only at screening for future research[4]

  *For **already included** patients (if (re-)consent is adequate):*
  - Isolated DNA 2-5 µg, viable cells/cell pellets, cytogenetic pellets, or (1-)3 unstained (or stained) BM smears of ***screening visit*** (preferred) or at least collected within +/- 3 months before or after diagnosis. Only in the cases that 'patients are not treated' or 'patients are only treated with EPO', samples within +/- 6 months before or after diagnosis.
- Flow cytometry (FCM): performed yes/no, if performed according to the ELN FCM WP8 platform: diagnosis

At each follow-up visit, including end of study

Follow-up data will be reported at 6-monthly intervals for all registered patients.

- Date of last visit prior to report
- Weight
- Karnofsky Performance Score, EQ-5D and VAS, MDS specific HRQoL (e.g. QUALMS-1*, to be implemented based on availability of language*).
- Changes in concomitant medical conditions and medication since last visit.
- Changes in MDS specific treatment since last visit:
  - Therapies for MDS.
    - if haematopoietic stem cell transplantation: date of transplantation; graft type and source donor cells/type of donor; response after transplantation: CR (yes/no), date of CR, date of relapse.
    - if (intensive) chemotherapy: start and stop date and type of chemotherapy (schedule), number of cycles; response: CR (yes/no), date of CR, date of relapse.

[4] Serum collection should be decided on at country or local site level. Logistics and storage of samples should also be arranged at country or local site level. This will no longer be coordinated centrally by the project management..

  - if use of hypomethylating agents (HMA): start date and type of agent; number of cycles, date of last HMA dose; response, according to revised Cheson criteria [37], date end of response according to Cheson revised criteria and/or physician.
  - Other therapies, including haematopoietic growth factors: start date and type of therapy; date of last dose; response, according to revised Cheson criteria [37], date end of response according to Cheson revised criteria and/or physician and date of first post-ESA transfusion due to MDS (excluding operations etc).
- Best supportive care (BSC, also when concomitant to other therapies for MDS).
  - red cell transfusion: date of first transfusion, number of transfusions since last visit, date of last transfusion and number of units transfused since last visit, pre-transfusion Hb value of last transfusion before visit, serum erythropoietin value with date if available.
  - if treatment with iron chelator is given: dose and schedule, start and stop date and type of therapy, duration, reason for discontinuation, ferritin values with date if available.

- Suspected Unexpected Serious Adverse Reaction (SUSAR) only in case if reported to local/national registries

- Laboratory values:
  - Peripheral blood: Hb concentration, white cell count, neutrophil, lymphocyte, monocyte, eosinophil and basophil count, platelet count, MCV, CRP, reticulocytes, glucose, albumin, LDH, liver transaminases, ferritin, erythropoietin, transferrin saturation level, serum creatinine and calculated creatinine clearance.
  - Bone marrow: date of BM aspirate and/or biopsy, percentage of blasts, percentage of ring sideroblasts, cytogenetics (karyotype).[5]

- Patient outcome:
  - number of transfusions (see above)
  - patients treated with interventional therapies, including haematopoietic growth factors (see above)
  - in case of MDS progression to a more advanced WHO-2008 / 2016 subtype / AML: provide the date of progression, WHO-2008 and 2016 classification.
  - in case of death: provide date and cause of death.

- ***Optional:*** Samples for biological correlative studies, including molecular studies:

  *For **all included** patients:*
  - 2 x EDTA-blood tubes (each 7 ml) for molecular analyses at ***follow-up visit***.
    Samples will be labelled only with EUMDS ID and date and time of sampling. *Collected samples for molecular analyses will be stored in the central tissue bank of the EUMDS Registry or can be stored in a local or in a national biobank if available.*

  *For **already included** patients with serum samples stored:*
  - ***Recommended:*** Continue extra serum sampling at each follow-up visit only for already included patients who have serum samples of (one or more) previous visits stored for future research.[5]

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.

[5] It is recommended to repeat bone marrow assessments (at the first follow-up visit) to confirm MDS diagnosis.

5. Ethics and GCP Compliance

Subject identification and protection

Patients are cared for according to their treating physician's best judgement. They are not be subjected to any experimental treatment or examination for the purposes of this study. The only exceptions are the PRO questionnaires and blood and / or bone marrow sampling for biological correlative studies, including molecular 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.

Version 5.1 of the protocol is reviewed by the Local, Regional or National Ethics Committees.

Informed Consent

All patients who are eligible for inclusion are informed of the aims and nature of the study. They are informed that all their clinical data 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 they can refuse participation at any time, without consequences for their further treatment. Documented informed consent will be obtained for all patients before they are registered. The informed consent procedure will be conform to the ICH guidelines on Good Clinical Practice (ICH-GCP) and will be in accordance with national and local regulatory requirements.

Human tissues collected in the context of this registration project will be used for scientific studies and genetic characteristics that play a role in MDS. Informed consent must be obtained for collection or 'further use' and storage of human tissues for ongoing or future research. The treating physician may inform the patient about new relevant information from this research which will affect their personal outcome in relation to their MDS. To ensure anonymity, all samples will be coded by the provider (or their staff) prior to transfer to the researcher.

Genetic or other types of research methods that might incur a risk of generating hitherto unknown congenital and clinically relevant findings about the current or future health of the patient can be considered. Efforts will be made to minimize the chance on these findings. An unsolicited finding policy will be implemented in compliance with Local, Regional or National regulatory requirements / ethical approval. Requirement will be established in a sample transfer agreement and registered in the database. Although policies might vary per country, in essence it should encompass informing the patient about the advantages and disadvantages of unsolicited findings, registration / policy for feedback of unsolicited findings to the patients (e.g. patients' preference). In the situation that a policy does not allow participation when the patient does not want to be informed, these samples will not be released for research using these research methods. In the situation that feedback is allowed / required, the researchers will inform the treating physician. The treating physician (with an ethicist/geneticist) will assess the importance of informing the patient. The patient's interest is paramount and overrides all other considerations.

For samples retrieved from biobanks, the policies of these biobanks will be adopted in line with requirements described above. For these samples approval by local or national research ethics committees will be required prior to release of samples.

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