



European MDS registry

A feasibility study

(As part of the EUMDS registry project)

Report status: final, 5 July 2007

Sponsor:

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Funded by *Novartis*

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Funded by Novartis

Acknowledgements

Manita Bremmers and Margo van Reen are acknowledged.

LIST OF ABBREVIATIONS..... 4

1 ABSTRACT 5

2 INTRODUCTION..... 6

2.1 OVERVIEW 6

 2.1.1 *Background* 6

 2.1.2 *The EUMDS registry*..... 7

2.2 OBJECTIVES OF THE FEASIBILITY STUDY..... 7

2.3 DECISION CRITERION..... 7

3 METHODOLOGY..... 8

3.1 INVESTIGATIONAL SITE QUESTIONNAIRE 8

 3.1.1 *Patient population and recruitment* 8

 3.1.2 *Present organization* 8

 3.1.3 *Organization for EUMDS registry*..... 8

 3.1.4 *Data entry/database* 8

 3.1.5 *Laboratory assessments* 8

 3.1.6 *Ethical Review*..... 9

 3.1.7 *General comments*..... 9

3.2 POSSIBLE PARTICIPANTS..... 9

3.3 ANALYSIS OF RESULTS 9

4 OUTCOMES AND EVALUATION..... 10

4.1 PATIENT POPULATION AND RECRUITMENT..... 10

4.2 PRESENT ORGANIZATION..... 11

4.3 ORGANIZATION FOR EUMDS REGISTRY 12

4.4 DATA ENTRY/DATABASE 12

4.5 LABORATORY ASSESSMENTS 13

4.6 ETHICAL REVIEW 13

4.7 GENERAL COMMENTS..... 13

5 PROJECT SCHEDULE 16

6 RECOMMENDATIONS..... 17

7 CONCLUSION..... 19

8 APPENDICES 20

8.1 APPENDIX 1: INVESTIGATIONAL SITE QUESTIONNAIRE..... 20

8.2 APPENDIX 2: TABLE 2: POSSIBLE PARTICIPATING CENTERS WITH PIS 20

8.3 APPENDIX 3: TABLE 3: PROPOSAL OF DISTRIBUTION OF NUMBER OF PATIENTS 20

APPENDIX 1 29

APPENDIX 2 31

APPENDIX 3:..... 32

List of abbreviations

AML	Acute Myeloid Leukemia
BM	Bone Marrow
EC	Ethical Committee
EUMDS	European MDS
GFM	Groupe Francais des Myelodysplasies
IPSS	International Prognostic Scoring System
MDS	Myelodysplatic Syndromes
PI	Principal Investigator
RA	Refractory Anemia
RARS	Refractory Anemia with Ringed Sideroblasts
RAEB	Refractory Anemia with Excess of Blasts
RCMD	Refractory Cytopenia with Multilineage Dysplasia
RCMD-RS	Refractory Cytopenia with Multilineage Dysplasia and Ringed Sideroblasts
WHO	World Health Organization

1 Abstract

Introduction:

This document reports the results and findings of the European MDS (EUMDS) feasibility study for the prospective, non-interventional multicenter European Registry on newly diagnosed MDS patients with IPSS low and intermediate-1.

Objectives:

The primary objectives of the feasibility study were:

- To determine the number of European referral centers interested to join the EUMDS registry
- To estimate how many eligible patients could be entered by each referral clinical center
- To assess whether the size of the study population (1000 to 2000 patients) was achievable within 18 months of inclusion

The secondary objective of this study was:

- To evaluate possible difficulties in organization of a EUMDS registry

Method:

It was decided that each referral center had to be visited and the principal investigator had to be interviewed carefully.

An investigational site questionnaire was prepared which was sent to participants 1 to 2 weeks preceding a visit to their center with an explicit request to prepare the required documents ready and to prepare the questions of the questionnaire to make the visit as useful as possible.

Results:

All 11 centers visited were interested in participation in the EUMDS project.

If circumstances are optimal it is estimated that 1423 patients per year can be included in the 11 countries that are interested to participate.

In these 11 countries in total, 147 centers will take part in the registry.

The major factor that could influence the recruitment positively was indicated by all referral centers: extra (budget for) personnel.

Conclusion:

The EUMDS project is feasible.

2 Introduction

This document reports the results and findings of the European MDS (EUMDS) feasibility study for the prospective, non-interventional multicenter European Registry on newly diagnosed MDS patients with IPSS low and intermediate-1.

The main part of the document details the background, method, findings, results, recommendations and conclusion. The appendices contain the feasibility questionnaire (appendix 1), list of principal investigators (PIs) (table 2, appendix 2), and a proposal for the distribution of number of patients that might be included (table 3, appendix 3).

The feasibility study is carried out to obtain information about number of referral centers that are interested in participating in the EUMDS registry, number of possible centers that might participate and an estimation of possible numbers of patients that can be included in the EUMDS registry.

The feasibility study is also performed to establish what kind of organizations, networks, knowledge, and infrastructure already exist, and how robust these organizations are. Because there is limited time and budget available for the EUMDS registry, elaborating on existing networks/organizations would be desirable.

This document enables discussion and decision-making by the Steering Committee regarding the future EUMDS project

2.1 Overview

2.1.1 Background

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.

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. Patients in the intermediate-2 or high-risk group are more likely to suffer from aggressive disease with higher frequency of transformation to acute myeloid leukemia.

2.1.2 The EUMDS registry

The EUMDS 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 this EUMDS project, data will be collected using registries in several European countries. This will create an international registry. The primary objective of the EUMDS registry is to describe the demographics and the disease management of newly diagnosed MDS patients within IPSS low and intermediate-1 categories classified according to the WHO criteria.

The secondary objectives of this EUMDS study are to investigate correlations between clinical characteristics, secondary iron overload and treatments received. The aim is to enroll a minimum of 1000 and a maximum of 2000 patients in the EUMDS registry during 18 months of inclusion.

Subsequently these patients will be followed for 5 years.

During the Steering Committee meeting of the 14th of September 2006, it was established that performing a feasibility study was necessary to determine the chance of success.

Novartis funded the feasibility study.

2.2 Objectives of the feasibility study

The primary objectives of the feasibility study were:

- To determine the number of European referral center interested to join the EUMDS registry
- To estimate how many eligible patients could be entered by each referral clinical center
- To assess whether the size of the study population (1000 to 2000 patients) was achievable within 18 months of inclusion

The secondary objective of this study was:

- To evaluate possible factors that might influence the success of the EUMDS registry. These factors included assessment of: different levels of already existing organizations, ethical committee procedures, experience with data entry, financial aspects, and laboratory analyses.

2.3 Decision criterion

The EUMDS study will be feasible when 1000 to 2000 patients can be included during the 18 months inclusion period.

3 Methodology

In order to be able to evaluate the plausible number of eligible patients per referral center, it was decided that each referral center had to be visited and the principal investigator had to be spoken with carefully.

An investigational site questionnaire was prepared which was sent to participants 1 to 2 weeks preceding a visit to their center with an explicit request to get the demanded documents ready and to prepare the questions of the questionnaire to make the visit as useful as possible.

3.1 Investigational site questionnaire

For the complete Investigational site questionnaire see appendix 1

3.1.1 *Patient population and recruitment*

The purpose of this important part of the questionnaire was to get an idea in what way the center concerned participated in any MDS projects before. Furthermore to be able to make an estimation of the number of patients included in MDS projects so far and more importantly estimating the number of patients that might be included in the EUMDS registry.

3.1.2 *Present organization*

This section of the questionnaire was added to be able to understand the organization of MDS projects already finished or still running. So differences or similarities between these projects could be detected and the chance of success concerning the EUMDS registry could be estimated.

3.1.3 *Organization for EUMDS registry*

The questions in this part of the questionnaire were recorded to obtain information how the organization for the EUMDS is intent to be in the center concerned and whether any additional needs are is needed.

3.1.4 *Data entry/database*

This section had to establish whether the necessary computer requisites were present at the different centers and where the data entry in each country would take place (central or local).

3.1.5 *Laboratory assessments*

This part had to give an impression whether all laboratory assessments could be performed at all centers. Furthermore to determine whether all the referral

centers were planning to review the bone marrow evaluations of other centers in the country.

3.1.6 Ethical Review

Each center should independently determine whether ethical review is required for participation in this registry. In general, regulatory authorities do not require ethical committee (EC) approval for observational registries of routine clinical practice. Therefore, the EC chairperson may choose not to conduct a full review of this EUMDS registry. This section is added to establish which countries have to submit the protocol of the EUMDS registry to an EC and to be able to determine what time is needed before the EUMDS registry can really start and furthermore to assess whether submission to one EC is sufficient for all participating centers in that particular country.

3.1.7 General comments

Finally this part was for the investigator for additional comments.

3.2 Possible participants

A preliminary survey conducted by Novartis/sponsor, has indicated that at least 11 countries throughout Europe would be interested in collaborating and enrolling patients in the EUMDS registry. These possible participating centers are represented by principal investigators (PIs). In table 2 in Appendix 2 the names of the PIs are listed.

3.3 Analysis of results

Given the nature of this study, the analysis was qualitative, examining

- The number of European referral centers interested to join the EUMDS registry
- Achievability of size of the study population (1000 to 2000 patients) per center and totally
- To determine possible difficulties in organization of a EUMDS registry

4 Outcomes and Evaluation

4.1 Patient population and recruitment

All referral centers visited participated, are still participating, or will participate in a regional or national MDS registry. Five countries have a national MDS registry namely France, Czech Republic (in combination with Slovakia), Greece, Spain, and Austria; Sweden will start a national registry in the beginning of 2008; The Netherlands, Germany, Great Britain, Rumania, Italy, and Greece have regional MDS registries.

All referral centers use some kind of database for data entry. These databases vary from an Oracle based database to SPSS based database and also web-based databases are used. The time that the referral centers are already using a database differs from over 10 years to less than one year.

The visit frequency is depending on the status of the patient in all centers visited and therefore varies between monthly to 3-4 monthly, but all centers can maintain appropriate follow-up.

A number of factors are indicated that might influence the inclusion:

- Financial support for
 - Translating protocol/patient information
 - EC procedures
 - Data management/data entry
 - Travel costs to visit other participating centers
 - Travel costs for personnel of referral center to attend operational team meetings
 - Training of new personnel
 - BM review in Sweden
 - A defined sum per patient 50% at enrollment and 50% at the end of the study or at death.
- Cytogenetics: in the local centers in the Netherlands cytogenetics are not performed for all patients, this depends on the treating physician and the age of the patient. The lack of cytogenetic results might negatively influence the recruitment.
- In Rumania cytogenetics are not performed yet. Personnel are trained already and a laboratory is available, only budget for equipment is lacking. When equipment is available cytogenetics will be performed for each new patient.

The number of patients that might be included in the EUMDS (table 1) was partly estimated and for the largest part based on data extracted from already existing databases with MDS-patients.

	Number of patients/year	Number of participating centers
Austria	50	2
Czech Republic	85	30
France	450	23
Germany	100	4
Great Britain	50	14
Greece	85	19
Italy	150	(15 -) 20
The Netherlands	65	18
Rumania	38	1
Spain	275	10
Sweden	75	6
Total	1423	147

Table 1: number of patients that might be included per year

Thus all referral centers are familiar with using a database, and all centers claimed to be able to maintain appropriate follow-up of the patients.

Furthermore a total of 1423 patients per year can be included in the EUMDS registry under ideal circumstances in a total of 147 centers.

4.2 Present organization

As described earlier in the majority of referral centers there is a regional or national MDS registry, and most countries have already established a network of participating centers. In some countries there even is a website with information about the network, participants, and protocol. A few referral centers perform the present MDS registry according to a protocol. In the greater part of the referral centers, the person who decides whether a patient is eligible for participating in a MDS registry is the principal investigator; in the other participating centers it ranges from principal investigator plus hematopathologist plus clinical hematologist, to principal investigator or treating physician or regional coordinator.

Data managers, study coordinators, research nurses and physicians perform the data entry; these persons are also responsible for any missing data.

In almost all referral centers people that are involved in the MDS registry had specific training.

The data entry can roughly be divided into two types.

- Central data entry performed by the referral center
- Local data entry performed by all participating centers in a certain country

At all centers the MDS status is determined according to WHO and FAB. In some registries the IPSS score is entered in the database or calculated by the database.

Thus according to the present organizations in the different countries, the level of organization differs but in the majority of participating countries there already is some kind of network, personnel of the referral centers that are involved in MDS registries are trained, have knowledge concerning MDS, and are experienced in obtaining missing data.

4.3 Organization for EUMDS registry

Eleven countries are interested in participating in the EUMDS registry. The number of centers that will participate in the EUMDS registry will vary per country and varies from 1 to 30 (see also table 1).

No important differences between the present MDS registries and the EUMDS registry have been reported. In the greatest number of referral centers, the dataset that has to be collected for the EUMDS registry is almost analogous to the dataset that has to be collected for the present MDS registry. The only important difference that has been reported twice is the difference in collection of follow-up data.

Comparable to the present organization, the one who decides whether a patient is eligible for participating in MDS registry ranges from principal investigator plus hematopathologist plus clinical hematologist, to principal investigator, regional coordinator or treating physician.

The IPSS score will be decided on by PI, calculated by database and checked by physician or data manager. Beside data entry in the central database, all data will be entered in databases for national or regional registries. No one foresees any problems for the entry in 2 different databases, except for the extra effort.

Requests have been made for the possibility for uploading data from national or regional databases to the central database. During the meeting of Steering Committee in Florence at the 16th of May 2007 it was decided not to upload any data to the central database because of uniformity of entered data.

Almost all referral centers will visit all participating centers to explain the EUMDS registry, except for France due to long distances. Sweden will make these visits only if funding for travel costs is available and also Greece would like travel budget.

All persons that will be involved in the EUMDS registry will receive training and all referral centers will send their coordinating personnel to operational team meetings, except for Greece. Furthermore some principal investigators remarked that personnel will be send to the operational team meetings only when needed and Austria even questioned the use of the operational team meetings.

4.4 Data entry/database

All referral centers are familiar with electronic data capture, are sufficiently equipped and have a helpdesk. Almost all referral centers use windows 2000 or windows XP. In Sweden besides Windows, MacIntosh based PCs are used. In Rumania only 1 PC is available for data entry.

France, Spain, and Czech Republic are planning a kind of quality control of the data that are entered at all the different centers. This means that after data are entered locally, the PIs in France, Spain, and Czech Republic will approve the data for evaluation by central data management by clicking a box.

Consistent with the organization for past or present MDS registries data entry will be performed according to one of the two types described at 4.2. Seven countries will perform data entry by the referral center namely: Greece, Sweden, the Netherlands, Great Britain, Italy, Düsseldorf and Rumania. In France, Czech Republic, Austria, and Spain each participating center will enter their own data.

4.5 Laboratory assessments

All centers can comply with all analyses needed, except for cytogenetics. In the Netherlands cytogenetics will only be performed at the referral center and at the other centers it will depend on the decision of the treating physician. In Rumania cytogenetics cannot be performed yet due to lack of equipment. Furthermore in Austria there is doubt about the necessity of the analysis of erythropoietin and due to the expensive analysis Austria is wondering whether erythropoietin will be assessed during each follow-up visit.

Concerning the bone marrow (BM) smear review, in the The Netherlands and Germany review of BM will be performed. In France each center will perform its own BM assessments. These centers are all member of the GFM group and are trained to perform the BM assessments. In Czech Republic, the 6 participating university centers will do the review of BM of the local hospitals. In Sweden where 6 university centers will participate, each university center will perform its own BM assessments. BM review in Sweden would be possible if budget for the review is available.

Great Britain prefers to perform BM review of all centers but this has to be discussed first.

The individuals who will examine and judge the BM vary between (hemato)pathologists and morphologists.

Unlike the other countries Greece specifically stated not to let the other centers know which patient has to visit for a follow-up.

4.6 Ethical Review

Except for two countries, in all countries approval of the one or more ECs is needed. Sometimes approval of only one central EC is needed, while in other countries besides approval of a central EC, approval of local EC of each participating center is needed. Besides approval of EC, approval of another committee is needed in France, Sweden, Italy, Great Britain, Austria, and Czech Republic. The time to approval of the EC varies from 6 weeks to 3 months.

Only in Czech Republic the total time to get approval of the EC and local committee can take 5-6 months.

In some countries a proposal for financial arrangements is required while in other countries a signed contract with the sponsor is necessary before submitment to the EC.

The fee for the EC varies between no fee to 1500-4000 euro.

4.7 General comments

The following remarks/requests/suggestions have been made

- Two referral centers (France and Czech Republic) made the request for uploading data from their own national registry database to the central EUMDS database. This would save a lot of time for the data manager, because data entry would have to be performed only once.

This request was already discussed during the Steering Committee meeting at the 16th of May 2007. The SC decided that all data have to be entered directly in the central database for uniformity.

- All referral centers indicated that the success of the EUMDS registry would absolutely increase when extra (budget for) personnel would be available. These extra personnel could be a research nurse, a data manager, or a coordinator.
Firstly extra personnel is needed in the referral centers to coordinate all the work in their and other participating centers, like translating the patient information, submitting the protocol and patient information to EC, distribution of the protocol over the participating centers, stimulating all persons involved in the EUMDS registry, data entry, when necessary training of new personnel, and coordinating the financial settlements with other participating centers.
Secondly extra personnel might be needed for participating centers for data entry.
It is clearly pointed out that when no funding for extra personnel is available, this might negatively influence the inclusion rate and also the amount of data that is entered in the database. Only Germany made very clear that even when no budget for extra personnel would be available, Germany would still start with the study.
- A request for a central login code with access to all the data of their country has been made by France, Czech Republic, Austria, and Great Britain. The former two referral centers reported to prefer performing of the quality control of the entered data at the referral center instead of by the central data management. The reason is that all the data entered locally are reviewed by the referral center before authorization, so in these referral centers there is a good overview of all the entered data and the possible question/remarks could be made in their own language. Therefore the error messages produced by the data management should be send to the referral centers in France and Czech Republic instead of to the participating centers in these countries. The other centers in these countries should only need a login code, which should give access to their own data.
- France indicated to prefer a contract of the sponsor with the GFM group of which Prof. P. Fenaux is the chair. All the participating centers are a member of the GFM group. The GFM group will draw up contracts with all the participating centers.
- Sweden would like to have a contract between the sponsor and Prof. E. Hellstrom. Stockholm will make all the arrangements with the other participating centers in their country.
- Some referral centers indicated to prefer a financial contract between sponsor and (department of) principal investigator directly without intervention of a financial department because otherwise a part (10-20%) of the money will be kept by the financial department
- A paper CRF is requested by Germany.
- Leeds reported the wish to download the data from the central database to their own database
- Czech Republic indicated that they would like the project management to submit the protocol to their EC for approval
- All principal investigators should be aware of the fact that this is a scientific investigator driven study, which will be partly funded by Novartis. The goal is to have budget for all activities that are performed especially for this study, for cost price.

- Austria proposed to build the database in such a way that only data entry is possible when all data of a patient are available (except for cytogenetics and epo) this will yield a database with only complete patients.
- Besides the numbers in table 1 Great Britain reported to have approached another 10 centers outside their region that might be interested in participating in the registry. For that reason Great Britain proposed a third type of organization/data entry for the EUMDS registry. This means that the referral center would perform data entry of the Yorkshire region by the referral center, while data entry of the remaining 10 centers would be performed locally. The referral center in Leeds would check all data entered by the remaining 10 centers. This would have major consequences for the amount of work for the referral site in Great Britain, for the different participating centers in Great Britain and Ireland and for the project management. Furthermore more contracts would have to be drawn up.
- Leeds would like to have a contract between the sponsor and Leeds for the participating centers in the Yorkshire region (14 centers) and single contracts between the sponsor and the other 10 centers in the UK and Ireland.
- Also Sweden indicated that all regional hospitals in the Nordic MDS group (which includes Denmark and Norway) might be enrolled when there is a fee per patient.

5 Project schedule

The feasibility study had to be completed within 3 months.

Preparation of feasibility questionnaire:	2 weeks	Before: May 2007
Review of questionnaire:	2 weeks	May 2007
Visiting 11 possible participating centers:	3months	end of June 2007
Writing feasibility report		July 2007
Review of report by sponsor		July 2007
Sending report to all members of steering committee and Novartis		July 2007

6 Recommendations

- There will be at least one coordinator per referral center for all practical/operational matters. This person will also attend the operational team meetings. Each center will send the name of the contact person to the project management before start of the study.
- A list of the names of all the participating centers in the different countries with a contact person per center will be sent to the project management before start of the study.
- Funding will be available for: EC fee, travel costs for visiting other participating centers, travel costs for attending the operational team meeting (at least one person per referral center), and coordinating personnel for referral centers.
- Contracts will be drawn up between sponsor and only one referral center per country. Each referral center will receive budget for a coordinating person; the budget will depend on the number of participating centers and on living standards/salaries of the different countries. Furthermore each referral center will receive fee per patient for 24 hours of data management for a complete patient, which will also depend on living standards of the different countries.
- A distribution of the number of patients (1000) has to be made in order to get included patients from all participating countries. All countries are allowed to try to include at least 50 patients during the first year of inclusion. A maximum number of patients that can be included per country have to be defined in the contracts. The proposed distribution is added in table 3 in appendix 3.
- During the first year of inclusion in total 1000 patients can be included in the EUMDS registry. The maximum number of patients that may be included per country is the number of patients that is mentioned in the contracts of the referral centers with the sponsor. When after one year of inclusion, less than 1000 patients are included, during the next 4 months of inclusion France, Spain, and Italy may include 80% of the remaining number of patients that can be included. The other countries together may include 20% of the remaining number of patients. The last 2 months of the inclusion period will be competitive with the number of patients that can be included depending on the decision that Novartis will made after the first year of inclusion. This means that the total number of included patients can either be 1000 or 2000. When this number is reached inclusion will be closed.
- The project management and the data management will make a proposal how the number of included patients for each can be controlled.
- The referral centers will make the necessary arrangements or contracts with the other participating centers in their own countries, according to agreements/requirements indicated by the sponsor.
 - The referral centers will be responsible for the distribution of (part of the) patient fee between the other centers, which take part in the EUMDS.
 - Each referral center will be responsible for submitment of the protocol, informed consent, and patient information to its own Ethical Committee or local ethical committee/other committees of other participating centers in their country.

- Each referral center, which performs data entry for all centers in their country, will have a login code with access to all data of their country or region for which central data entry is performed. The referral centers in France, Austria, Spain, and Czech Republic will have login codes with access to all data of their country. Furthermore there will be a login code for the principal investigators in referral centers to approve the data entry of the other participating centers in their countries. The other centers in France, Austria, Spain, and Czech Republic will have login codes with only access to their own data.
- The quality control will be completely performed by the central data management in York. They will send emails to the centers, which entered the data. In case of France, Austria, Spain, and Czech Republic, the referral centers will receive a copy of these emails.
- Create a page for the EUMDS registry on the ELN website with PDFs of CRF, patient information, protocol, recent minutes of Operational Team and Steering Committee
- Although in some countries no approval of the ethical committee is needed, informed consent of each patient in each country should be mandatory as written in protocol.
- Start with ethical committee procedures in each country as soon as possible, after contract between Novartis and sponsor is signed.

7 Conclusion

- The first goal of the feasibility study was to establish the number of referral centers that are interested in participating in the EUMDS. All 11 visited centers are definitely interested in joining the EUMDS registry.
- The second objective of this feasibility study was to make an estimation of the number of patients that can be included in the EUMDS registry during 18 months of inclusion
The total number of patients that can be included during 18 months is 2134 in 147 different centers, but only if the circumstances are optimal.
- The secondary objective of this study was to evaluate possible difficulties in the EUMDS registry. The factors that were established to influence the recruitment were:
 - Lack of financial support for coordinator/researchnurse/datamanager
 - Assessments of cytogenetics not always performed in all centers in The Netherlands and not yet performed in Rumania
- Although currently there is a different level of organization in the different countries, the present networks can be used as a basis for the EUMDS registry.

8 Appendices

- 8.1 Appendix 1: Investigational Site Questionnaire**
- 8.2 Appendix 2: Table 2: Possible participating centers with PIs**
- 8.3 Appendix 3: Table 3: Proposal of distribution of number of patients**

Appendix 1

The study objectives of EUMDS are:

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

The sponsor of the registry is prof. T. de Witte of the University Medical Center Nijmegen.

This Investigational Site Questionnaire is a part of the feasibility study. The sponsor is currently evaluating Investigators who will participate in EUMDS.

The goals of this feasibility study are:

- To evaluate a number of European Referral clinical sites interested to join the European MDS Registry project
- To evaluate how many eligible patients could be entered by each Referral clinical site.

In view of your experience, we invite you to complete the following questionnaire. Please complete the entire questionnaire and attach any applicable documents/policies, if needed.

PRINCIPAL INVESTIGATOR _____

NAME OF INSTITUTION _____

MAILING ADDRESS _____

CITY _____ ZIP _____

TELEPHONE NUMBER _____ FAX _____

E-MAIL ADDRESS _____

STUDY COORDINATOR OR RESEARCH CONTACT PERSON _____

TELEPHONE NUMBER _____ FAX _____

E-MAIL ADDRESS _____

CONTRACT CONTACT PERSON _____

TELEPHONE NUMBER _____ FAX _____

E-MAIL ADDRESS _____

Appendix 1

PATIENT POPULATION AND RECRUITMENT:

- a. Did you participate in a MDS registry before? Yes No
 If yes, can you please attach the protocol(s) of the registry(s) and give the name(s) of the registry(s) _____
-
- b. Do you have a database with MDS patients that participated in earlier registries? Yes No
- c. Can you make a query from your database of all the included encoded MDS-patients per registry per year? Yes No
 If yes, can you please attach a list of included encoded MDS-patients?
- d. Are all the patients in the attached list from your site? Yes No
- e. If no, how many other sites participate in your MDS registries? _____
 If no, can you please attach a list with names and addresses of the other participating sites.
 If no can you please make a query from your database of the included encoded MDS patients sorted per site and per year and attach this query?
- f. Can you make a query from your database of the included encoded patients per year per site with their IPSS classification per site? Yes No
 If yes, please attach a list of included encoded patients with their IPSS classification.
- g. Do you have contracts of registries? Yes No
 Can you show us contracts of these registries at our visit?
- h. Please complete this question based on your experience enrolling to other MDS registries:
 How many patients with IPSS low or intermediate-1 MDS ≥18 years did you recruit (on average) in the last registry?
 Subjects from your site in total during registry period of months.
 Subjects from other participating sites in total during registry period of months
- i. Did your site reach the recruitment target in that registry? Yes No
- j. Which criteria (please Refer to Appendix 1
- k. ATTACHMENT 1:) will most likely limit recruitment at your site for the EMDS registry?
 Inclusion criteria Nr.: _____ Comment why: _____

 Exclusion criteria Nr.: _____ Comment why: _____
- l. Are you/will you be conducting any other registries in this specified subject population in the period between: 2007 and 2014 Yes, please specify the number of registries _____ No.
- m. Will any of these registries compete for enrollment with the EMDS registry? Yes No
- n. Does your facility see enough patients so that both protocols can be conducted without affecting either's enrollment expectations? Yes No
- o. Based on your review of the attached eligibility criteria, how many subjects do you anticipate enrolling in the EMDS registry in your site? Subjects per year
- p. Based on your review of the attached eligibility criteria, how many subjects do you anticipate enrolling in the EMDS registry in possible other sites in your country? Subjects per year
- q. How frequently do MDS patients visit your clinic?
 Monthly
 Every six months
 Every year
 Other, please specify
- r. How frequently do MDS patients visit the clinic in the other participating sites?
 Monthly
 Every six months
 Every year

Other, please specify

Appendix 1

- s. Can appropriate follow up be maintained (every 6 months) at your site? Yes No
- t. Can appropriate follow up be maintained (every 6 months) at the other sites? Yes No
- u. Can you think of any factors that may influence the recruitment of patient for MDS registries at your site or other sites that were participating in former registries? Yes No
 If yes, can you please explain: _____

PRESENT ORGANISATION

- a. Do other sites in your country send the data of patients directly to your site? Yes No
- b. Do other sites in your country have their own registry Yes No
- c. Who is responsible for the protocol and registration forms at your site? Can you please describe _____
- d. Who is responsible for the protocol and registration forms at the other participating sites? Can you please describe _____
- e. Do you have any correspondence with other sites regarding protocol(s) of other MDS registries? *Can you show us at our visit?*
- f. Who decides whether a patient is eligible for participating in a MDS registry at your site? Can you please describe _____
- g. Who decides whether a patient is eligible for participating in a MDS registry at the other participating sites? Can you please describe _____
- h. Who examines the bone marrow (BM) smear and biopsy at your site? Can you please describe _____
- i. Who examines the BM smear and biopsy at the other participating sites? Can you please describe _____
- j. Who is responsible for entering the data of an included patient to the MDS database at your site? Can you please describe _____
- k. Who is responsible for entering the data to the MDS database at the other participating sites? Can you please describe _____
- l. Is your site responsible for entering the data of patients who visit other sites to the MDS database?
- m. Who is responsible for any missing data at your site? Can you please describe _____
- n. How has the person described at the previous question obtained the missing data at your site? Can you please describe _____
- o. Who is responsible for any missing data at the other participating sites? Can you please describe _____
- p. How has the person described at the previous question obtained the missing data at the other participating sites? Can you please describe _____
- q. Have the persons involved in your MDS registries had any specific training? Yes No
- r. Do you think your site is sufficiently equipped to conduct the present MDS registries? Yes No
- s. If no, can you please explain what extra equipment or personnel you would like to have? _____
- t. Does your site determine the MDS status according to the FAB classification? Yes No
- u. Does your site determine the MDS status according to the WHO classification? Yes No

ORGANISATION FOR EUMDS REGISTRY

- a. Can you think of and describe any important differences between MDS registries already running and the EMDS registry?

Appendix 1

- b. Will other sites in your country send the patients for the EMDS registry directly to your site?
- c. Who will decide whether a patient is eligible for participating in the EMDS registry at your site? Can you please describe _____
- d. Will your site perform a review of the BM smear and biopsy of MDS patients from other participating site?
- e. Who will decide whether a patient is eligible for participating in a MDS registry at the other participating sites? Can you please describe _____
- f. Who will decide what IPSS score a patient has at your site? Can you please describe _____
- g. Will your site decide what IPSS score a patient from other participating sites has? Yes No
- h. Who will be responsible for entering the data of an included patient to the MDS database at your site? Can you please describe _____
- i. Will the data of the patients of the EMDS registry also be entered in a national registry? Yes No
- j. Do you foresee any problems for the entry of data in 2 different databases? Yes No
- k. If yes can you please specify _____
- l. How will you obtain all the data from other participating sites? Can you please describe _____
- m. When data from other participating sites are missing, how will the responsible person from your site obtain these data? Can you please describe _____
- n. Who will be responsible for any missing data at your site? Can you please describe _____
- o. How will the person from the previous question obtain the missing data? Can you please describe _____
- p. Will you plan visits to other sites to explain the EUMDS registry? Yes No
- q. Will you plan visits to other sites to obtain patient data? Yes No
- r. Will the persons who will be involved in your EUMDS registries get any specific training? Yes No
- s. If _____ yes, _____ can _____ you _____ please _____ describe _____
- t. Do the persons involved in your EMDS registry need any further specific training? Yes No
- u. If yes can you please describe _____
- v. Would your centre wish to send key personnel to the operating team meetings? Yes No

Appendix 1

DATA ENTRY/DATABASE:

The sponsor is planning to use computerized electronic data capture to collect study data. Electronic Data Capture (EDC) involves entering study data onto an electronic web based CRF (e-CRF) which is then transferred over the Internet to CDMSU (Central Data Management and Statistical Unit). CDMSU and Project Management representatives will work with you to properly train your site for EDC.

- a. Does anyone within your research group have experience with data collection using a computerized electronic data capture (EDC) system? Yes No
- b. Do you have PCs available at your site to enter subject data for this registry? Yes No
- c. Do you have an Internet connection for these PCs? Yes No
 - If yes, please specify:
 - Dial up connection (e.g. 56K modem) Yes No
 - Cable, ADSL, ISDN Yes No
 - Hospital network Yes No
 - Other (please _____ specify):
- d. Which browser and which version do you use? Can you please specify:
- e. Which version of windows do you use? Can you please specify:
- f. Would you allow the monitor to connect to the Internet during the monitoring visits? Yes No
- g. Do you have IT (computer) support at your site (e.g., Helpdesk)? Yes No
- h. Are you willing to enter the results of the possible other sites of your country to the eCRF? Yes No
- i. Please describe how you are planning to enter the data to the eCRF (from handwritten entries, paper registration forms, locally created forms, status of patient, local database output, etc.)

- j. Would you like specific graphics or possibilities for queries to be built in to the database? Please specify:

LABORATORY ASSESSMENTS

Please see attached laboratory assessments Appendix 1
 ATTACHMENT 2: Can your center comply with these analyses?

- a. If no can you please specify which analyses you are not able to perform:

- b. Can other participating sites comply with these analyses? Yes No
- c. If no please can you please describe which site is not able to perform which analysis

- d. Does your site perform any assessments mentioned in Appendix 1
- e. ATTACHMENT 2: for other sites?

If	yes,	<input type="checkbox"/>	can	Yes	you	<input type="checkbox"/>	please	No specify
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- f. Does your site have facilities to evaluate BM aspirates Yes No
- g. Does your site have facilities to perform cytogenetic assessments in BM aspirate Yes No
- h. Do the other participating sites in your country have experience with cytogenetic assessments in BM aspirate
- i. Does your site perform cytogenetic assessment for each new patient without regard to age? Yes No
- j. Are you willing to perform cytogenetic assessments in BM aspirate for each newly included patient? Yes No

Appendix 1

- k. Does your site perform primary evaluation of BM aspirates for possible other sites? Yes No
- l. Does your site review evaluation of BM aspirates for possible other sites? Yes No
- m. Does your site perform primary evaluation of BM biopsies for possible other sites? Yes No
- n. Does your site review evaluation of BM biopsies for possible other sites? Yes No
- o. If yes, does the reviewer have adequate data of laboratory values, clinical information and cytogenetic results that are necessary to classify MDS according to the WHO classification and IPSS score?
- p. Are you willing to review all the BM aspirates and BM biopsies for the other sites in your country?
- q. If yes, can you please explain how the BM aspirates and biopsies will be send to you and when you will analyze the BM
Preferable blank smears
-

r. Which staining methods will you use for the BM?

s. Who will judge the BM at your site?

t. Who will judge the BM at the other sites? _____

u. Can you show us some samples of BM at our visit to your site? Yes No

v. Are you willing to let the possible other sites in your country know, which patient has to visit the centre for follow up?
 Yes No

Appendix 1

INSTITUTIONAL REVIEW BOARD (IRB)

- a. Does this EUMDS registry have to be approved by a review board in your country? Yes No
- b. If no, please go to OTHER COMMITTEES
- c. Do you have a central local or a central IRB?
 Local Central Both
- d. Please note the name and address of the IRB _____
- e. How often (*please note dates if available*) does your IRB meet? (*i.e. weekly, monthly, bi-monthly*)

- f. How long prior to the meeting date the IRB submission documents must have been received?
- g. ___ Week(s)
- h. Are there any months/periods that the IRB does not meet? Yes No (explain):

- i. How long does the IRB approval process (i.e., from submission to written approval letter) take at your site? Best-case scenario: ___ weeks/months Worse Case scenario: ___ weeks/months
- j. Comments: _____
- k. Can you submit this EUMDS registry to the IRB when contract with the sponsor is not signed yet? Yes No
- l. Do the other sites have to submit the protocol to their own IRB Yes No
- m. Is approval of your IRB sufficient for the EUMDS registry to be performed at all possible sites in your country? ___

OTHER COMMITTEES:

- a. In addition to the IRB, does your site require approval from any other committees/groups (e.g., scientific committee, hospital board, local regulatory agency)? No Yes, please specify committees _____

Appendix 1

GENERAL COMMENTS:

Completed by:

(Name)

(Signature)

(Function/role)

(Date)

Appendix 1

ATTACHMENT 1: SUMMARY OF MOST IMPORTANT INCLUSION/EXCLUSION CRITERIA:

Patients must meet all of the following criteria to be included in the EMDS registry:

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

Subjects meeting any of the following criteria may not be enrolled in the study:

1. Age < 18 years
2. Patient unwilling or unable to give informed consent
3. Intermediate-2 or higher risk MDS
4. Secondary/therapy-related MDS

Appendix 1

ATTACHMENT 2:

Laboratory assessments	Study visit	
	Inclusion	Follow-up (every 6 months)
Height	x	
Weight	x	x
Karnofsky Performance Status, I-ADL	x	x
ECG, echocardiography, LVEF*	x	x
Laboratory values: peripheral blood		
Hb, MCV, WBC + differential, RBC, platelets, reticulocytes	x	x
Glucose	x	x
ALAT, ASAT, Alk Phosphatase, LDH, bilirubin (total and indirect)	x	x
Serum creatinine and calculated creatinine clearance	x	x
Ferritin, iron saturation level	x	x
Erythropoietin	x	x
Laboratory values: bone marrow		
Date of bone marrow aspirate and/or biopsy	x	x
% blasts	x	x
Cytogenetics	x	x
Laboratory values: urine		
Urinalysis for protein (dipstick)	x	x

* These data will be collected in ancillary studies in a subset of patients.

Appendix 2

Austria:	Prof. M. Pfeilstoecker
Czech Republic:	Dr. J. Cermak
France:	Prof. P. Fenaux
Germany:	Dr. U. Germing
Great Britain:	Prof. D. Bowen
Greece	Prof A. Symeonidis
Italy:	Prof. L. Malcovati
The Netherlands:	Prof de Witte/ Dr. M. MacKenzie
Rumania:	Prof. R. Gologan
Spain:	Prof. G. Sanz
Sweden:	Prof. E. Hellstrom-Lindberg

Table 2: Possible participating centers with PIs

Appendix 3:

Country	Estimated number of patients that can be included	Proposed number of patients allowed to be included
Austria:	50	50
Czech Republic:	85	70
France:	450	239
Germany:	100	80
Great Britain	50	50
Greece	85	70
Italy:	150	120
The Netherlands:	65	60
Rumania:	38	50
Spain:	275	146
Sweden:	75	65
<i>Total</i>	<i>1423</i>	<i>1000</i>

Table 3 Proposal of distribution of number of patients that may be included per country during the first year

Estimated number	Proposed number	Proposed factor
<50-50	50	na
50-150		0.8-0.9
>150		0.53

Table 4: used factors for table 3