Registry of the
European Working Group (EWOG)
of Myelodysplastic Syndrome (MDS)
in children and adolescents

EWOG-MDS Registry

Version 2.1

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EWOG-MDS Coordinating Investigator

Prof. Dr. Miriam Erlacher
Department of Pediatrics and Adolescent Medicine
Ulm University Medical Center
Eythstraße 24, D-89075 Ulm, Germany

Tel: (+49) 0731 500 57001
E-mail: miriam.erlacher@uniklinik-ulm.de

EWOG-MDS Coordinating Study Center

Site Ulm
Department of Pediatrics and Adolescent Medicine
University Medical Center Ulm
Eythstraße 24, D-89075 Ulm, Germany
Tel: (+49) 0731 500 57001
E-mail: ewog-mds@uniklinik-ulm.de

Site Freiburg
Division of Pediatric Hematology and Oncology
Department of Pediatrics and Adolescent Medicine –
University of Freiburg Breisacher Straße 62, D-79106
Freiburg, Germany
Tel: (+49) 0761 270 43645

E-mail: ewog-mds-saa@uniklinik-freiburg.de
www.ewog-mds-saa.org

Approval of the Registry

Title:

Registry of the European Working Group (EWOG) of Myelodysplastic Syndromes (MDS) in Children and Adolescents (EWOG-MDS)

The following persons declare their consent with the registry protocol:

EWOG-MDS Coordinating Investigator	20.07.2026	
Name Prof. Dr. Miriam Erlacher	Date	Signature

National Coordinator of EWOG-MDS in XXX *(country)*		
Name XXX	Date	Signature

List of Abbreviations

AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ASXL1	Additional sex combs-like 1
ATG	Anti-thyomcyte globulin
CBL	Casitas B-lineage lymphoma
CRF	Case report form
CIR	Cumulative incidence of relapse
CSC	Coordinating study center
DEB	Diepoxbutan
DLI	Donor lymphocyte infusion
DRKS	German Clinical Trials Register
EWOG	European Working Group
eCRF	Electronical case report form
ERCC6L2	ERCC excision repair 6 like 2
ETV6	ETS Variant Transcription Factor 6
EFS	Event-free survival
FISH	Fluorescence in situ hybridization
FDA	US Food and Drug Administration
GATA2	GATA-binding factor 2
GCP	Good clinical practice
GVHD	Graft-versus-host disease
GVL	Graft-versus-leukemia
Haplo	Haploidentical donors
HSCT	Hematopoietic stem cell transplantation
IBMFS	Inherited bone marrow failure syndrome
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IST	Immunosuppressive Therapy
JMML	Juvenile myelomonocytic leukemia
KRAS	Kirsten rat sarcoma viral oncogene
MDS	Myelodysplastic syndrome
MDS-EB	MDS with excess blasts
MMC	Mitomycin C
MPD	Myeloproliferative disorder
MUD	Matched unrelated donor
MSD	Matched sibling donor
NF1	Neurofibromatosis type 1
NRAS	Neuroblastoma RAS Viral (V-Ras) Oncogene
NS	Noonan syndrome
NRM	Non-relapse mortality
PTPN11	Protein tyrosine phosphatase non-receptor type 11

qPCR	Quantitative polymerase chain reaction
PIC	Patient information sheet and the Proposed Informed Consent
RAS	Rat sarcoma
RCC	Refractory cytopenia of childhood
RUNX1	Runt-related transcription factor 1
SAA	Severe aplastic anemia
SAMD9	sterile alpha motif domain containing 9 like
SAMD9L	sterile alpha motif domain containing 9
SETBP1	SET binding protein 1
SH2B3	SH2B Adaptor Protein 3
SOP	Standard operating procedure
TBI	Total body irradiation
TP53	Tumor suppressor 53

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Synopsis

TITLE	Registry of the European Working Group of Myelodysplastic Syndrome (EWOG-MDS) in children and adolescents
ABBREVIATED TITLE	EWOG-MDS Registry
REGISTRY NUMBER / DRKS	will be applied for
INDICATION/ MAIN DIAGNOSIS	• Myelodysplastic syndrome (MDS) • Refractory cytopenia of childhood (RCC) • Myelodysplastic/myeloproliferative disorders (MDS/MPD) including juvenile myelomonocytic leukemia (JMML) • Genetic conditions predisposing to these disorders
OBJECTIVES	• To continuously register all individuals with newly diagnosed RCC, MDS, MDS/MPS or genetic predisposition for these disorders (incidence) • To document the initial diagnostic work-up in reference laboratories • To document their clinical characteristics, treatment and outcome data (hematological and non-hematological phenotype, treatment decisions, treatment, follow-up health status, survival) • To assess biological disease features and correlate them with genetic, clinical and outcome data (prognostic markers) • To assess social determinants of health and correlate them with clinical, psychosocial, geographic and quality of life parameters (health equity, inclusion)
DESIGN	International prospective multicenter registry
PARTICIPATING CENTERS	Departments of Pediatric Oncology and Hematology in Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Ireland, Israel, Italy, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and Switzerland.
RECRUITMENT	Continuous prospective registration and follow-up Retrospective registration after approval by the EWOG-MDS coordinating investigator and the respective National Coordinator
INCLUSION CRITERIA	• Confirmed diagnosis of MDS, RCC, MDS/MPD including JMML in patients < 21 years • Diagnosis of a germline condition predisposing to these disorders in individuals of all ages • Patients (or their legal representatives) having provided informed consent
EXCLUSION CRITERIA	• No written consent available • Severe aplastic anemia (SAA) registered in EWOG-SAA • RCC in the classical inherited bone marrow failure syndromes (IBMFSs) Fanconi anemia, dyskeratosis congenita, severe congenital neutropenia, Shwachman-Diamond syndrome, Diamond-Blackfan anemia syndrome, and Pearson syndrome • Transient myeloproliferative disorder in Down syndrome, myeloid neoplasms associated with Down syndrome • Classical myeloproliferative neoplasm like chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, primary myelofibrosis, chronic eosinophilic leukemia
DATA COLLECTED	• Diagnostic features • Clinical characteristics, disease status • Treatment decisions and applied therapy • Longitudinal health status and interventions • Psychosocial characteristics, quality of life parameters • Treatment Outcome and Survival
STATISTICAL ANALYSIS	Descriptive statistical analysis will be performed annually
ETHICAL CONSIDERATIONS	• In the absence of a specific legal framework for clinical registries the registry is set up according to the declaration of Helsinki of the WHO and the International Conference on Harmonisation Guideline for Good Clinical Practice (ICH-GCP) • Participating centres must have/apply for local ethics approval • Patient registration requires a consent specific for the EWOG-MDS registry • Storage of biomaterial in the national biobanks is independent of the registry and requires an additional specific consent

1 Background

1.1 The Rational (Need for the project)

Myelodysplastic syndrome (MDS), refractory cytopenia of childhood (RCC), and myelodysplastic/myeloproliferative disorders (MDS/MPD) including juvenile myelomonocytic leukemia (JMML) belong to a rare spectrum of myeloid disorders presenting in children and adolescents. The rarity, the lack of standardized unequivocal diagnostic tests and the broad differential diagnosis including severe aplastic anemia (SAA), reactive bone marrow changes, and acute myeloid leukemia (AML) are a major challenge for the work of researchers and physicians aiming to elucidate the disease characteristics, the molecular biology, the genetic background, and the clinical course. Studies performed by the European Working Groups of MDS in Childhood (EWOG-MDS) and SAA in Childhood (EWOG-SAA) have resulted in significant improvement in classification of this group of disorders, a better understanding of their molecular biology, the development of risk-based treatment strategies and in consequence improved cure rates for the affected children and adolescents.

A clinical registry offers the chance to collect clinical data continuously in order to better describe the epidemiology, disease characteristics and clinical outcomes and serve as a platform for the development of clinical trials. Furthermore, the combination with biomaterials stored in a biobank will allow the development of new diagnostic tools and facilitate specific research projects for these unique disorders.

1.2 The European Working Groups of MDS and SAA in Children and Adolescents

Within EWOG-MDS and EWOG-SAA, physicians and researchers from the different areas have long worked together with the aim to a) elucidate the pathophysiology and the natural history of these rare disorders b) increase the number of patients cured from the disease, c) decrease acute and chronic side effects of therapy needed, d) study innovative therapy approaches and e) inform patients about our current understanding of their disease at any time.

EWOG-MDS was founded in 1993 by members from Austria, Czech Republic, Denmark, Germany, Italy, and the Netherlands and later joined by Belgium, Finland, Greece, Hungary, Ireland, Israel, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and Switzerland. In 2007, EWOG-SAA was established involving the same countries participating in EWOG-MDS. The “EWOGs” are intended to grow and are open to other participants.

The backbone of the groups is a network of National Coordinators in the different countries participating in EWOG-MDS and EWOG-SAA. They are responsible for implementing the groups’ aims, registries and studies in their respective countries. In general, a National Coordinator is designated by his/her National Pediatric Oncology Association. National Coordinators ensure registration in the EWOG-MDS registry and are responsible for the national data-collection and transfer of the data to the groups’ Study Coordinating Center (CSC). The CSC is currently located at the University Children`s Hospital, Freiburg in Germany and the Department of Pediatrics and Adolescent Medicine at Ulm University Hospital in Germany. Diagnostic data are collected from the established national reference centers for morphological, histological, cytogenetic and molecular studies. National Coordinators are responsible for providing access to the national reference laboratories and support participating centers by communicating recommendations for diagnostic procedures and possible treatment recommendations. The latter activities are independent of the EWOG-MDS registry.

1.3 The Diseases

1.3.1 Definitions and Diagnosis

- ***Myelodysplastic syndrome (MDS)***

Myelodysplastic syndrome (MDS) is an acquired clonal hematopoietic stem cell disorder characterized by ineffective hematopoiesis, as evidenced by cytopenias, morphologic dysplasia, and risk for progression to acute myeloid leukemia (AML).[1] MDS in children and adolescents can either arise *de novo* or develop after antecedent or predisposing conditions, including certain germline mutations, inherited bone marrow failure syndromes (IBMFSs), prior chemotherapy/radiation therapy (therapy-related MDS), or acquired severe aplastic anemia.[2]

Like in adults, MDS in pediatric patients is classified according to international consensus classification systems. Cases with a histopathological pattern of RCC (see below) are the most common form of MDS in children and adolescents.[3,4] Pediatric MDS with excess blasts (MDS-EB) is defined as MDS with 5-19% blasts in the bone marrow or 2-19% blasts in the peripheral blood.[1] However, genetic lesions or clinical course rather than a fixed threshold of blast percentage best separate MDS from AML.[5,6] The most frequent chromosomal aberrations are monosomy 7, trisomy 8 and complex karyotype; chromosomal translocations are unusual.[7] Somatic mutations in genes of epigenetic regulation or RNA splicing are rare, instead, mutations in *SETBP1*, *ASXL1*, *RUNX1* and the RAS/MAPK pathway mutations are the most common somatic aberrations.[8] In *de novo* MDS-EB, tandem duplications in *UBTF* are detectable in bone marrow cells of a relevant number of patients[9], while *TP53* mutations are frequently observed in therapy-related MDS[10,11].

- ***Refractory cytopenia of childhood (RCC)***

Refractory cytopenia of childhood (RCC) is characterized by persistent cytopenia, dysplasia, a normal blast percentage, and a distinct hematopathological pattern.[1,2] RCC was included in the 4th WHO classification of tumors of hematopoietic tissue to capture pediatric bone marrow patterns that might progress to MDS or to severe bone marrow hypoplasia.[3] RCC represents a biological spectrum of disease stages reflecting the plasticity of the bone marrow in children. While some cases of RCC are bona fide MDS, others may lack evidence of clonality.

The majority of patients with RCC present with a hypocellular bone marrow.[4] Marrow architecture is disturbed with patchy distribution of hematopoiesis, predominance of erythropoiesis with dysplastic features and impaired maturation, and significantly reduced granulopoiesis and megakaryopoiesis.[2] Most patients with RCC have a normal karyotype in hematopoietic cells.[4,12] Monosomy 7 is the most common cytogenetic aberration.[13,14] Currently, approximately 20% of RCC cases are known to have an underlying germline predisposition like GATA2 deficiency, SAMD9/SAMD9L syndrome, or RUNX1 deficiency.[2,15,16]

- ***Myelodysplastic/myeloproliferative disorders (MDS/MPD) including juvenile myelomonocytic leukemia (JMML)***

Hematopoietic disorders with both myelodysplastic and myeloproliferative features (MDS/MPD) comprise a broad phenotypic spectrum of diseases in pediatric patients.[17] Juvenile myelomonocytic leukemia (JMML) is a unique clonal hematopoietic neoplasm with MDS/MPN overlap features.[18,19] Neoplasms arising in patients with predisposition syndromes or prior chemotherapy/radiation therapy can also present as MDS/MPD.[20] In some young infants with Noonan syndrome[21-24] and in neonates with germline mutations in *SH2B3*[25-27], a transient MDS/MPD overlap disorder lacking signs of clonality is noted. While morphology is an important tool in establishing the diagnosis of MDS/MPD, the identification of the major genetic pathway implicated in the pathogenesis is required to identify the distinct nature of the disorder.

JMML is characterized by constitutive activation of the RAS signal transduction pathway. About 95% of patients harbor molecular alterations in one of five genes (*PTPN11*, *NRAS*, *KRAS*, *NF1* or *CBL*), which define genetically and clinically distinct subtypes.[18,28] One of these canonical activating RAS pathway mutation is sufficient to cause JMML. Two of the five major subtypes are characterized by germline events in either *NF1* or *CBL* that progress to neoplasia with acquired biallelic inactivation of the respective genes in hematopoietic cells. The other subtypes, *PTPN11*, *NRAS*, and *KRAS*

mutated JMML, are characterized by heterozygous somatic gain-of-function mutations in children without germline disease. Secondary mutations are present in about one-third of cases.[29-32] Genome-wide DNA methylation analysis identified three methylation subclasses with unique molecular and clinical characteristics.[32-35]

- ***Genetic conditions predisposing to MDS, RCC and MDS/MPD***

Germline cancer predisposition is identified in an increasing subset of pediatric patients with MDS, RCC and MDS/MPD.[2] The rapidly increasing list of genes with predisposing germline genetic alterations include *GATA2*, *SAMD9/SAMD9L*, *RUNX1, ETV6, ERCC6L2* and others. It is appreciated that these predisposition syndromes with highly variable phenotypes may present with hematological signs without any overt syndromic features.

In patients with MDS, RCC and MDS/MPS and an underlying germline predisposition, it is standard practice to test potential family donors for allogeneic hematopoietic stem cell transplantation (HSCT) for presence of the respective genetic condition.[36] The natural history of individuals with germline predisposition to myeloid neoplasms without hematological signs or symptoms is largely unknown.[37] To foster knowledge in the rare germline cancer predisposition underlying pediatric MDS, RCC and MDS/MPD, patients and individuals with of one of these genetic conditions can be included in this registry in the absence of MDS, RCC or MDS/MPD.

Note: It is appreciated that not all individuals with a genetic predisposition to MDS, RCC or MDS/MPD require medical care for their susceptibility and are thus not patients in a narrower sense of the term. For the purpose of easy readability of this document, these individuals are here included in the term patients in paragraphs 2-10 of this text.

1.3.2 Hematopoietic Stem Cell Transplantation

Allogeneic hematopoietic stem cell transplantation (HSCT) is the therapy of choice for the majority of children and adolescents with MDS, RCC and MDS/MPN and is generally available in countries with high resources.[12,38,39] Outcome following HSCT is in large part dependent on the nature of the disorder treated; prognostic parameters are blast percentage, marrow cellularity, karyotype, and presence/nature of somatic mutations. Preparative regimens including total body irradiation (TBI) are generally avoided due to severe late effects in young individuals.[40,41] Intensity of immunosuppressive therapy is in large part dependent on the risk of disease recurrence after HSCT.

The three main types of donors, HLA-matched sibling donors (MSD), matched unrelated donors (MUD), and haploidentical donors (Haplo), each have advantages and disadvantages in terms of HLA compatibility, waiting time for HSCT, and risk of complications. Most patients diagnosed in Europe are transplanted from a MSD or MUD; event-free survival (EFS) for children with MDS, RCC and MDS/MPD is compatible for both donors.[12,38,42] In HSCT with an MUD, serotherapy like antithymocyte globulin is often included. Some investigators pioneer Haplo HSCT, while others choose a haploidentical donor in the absence of a MSD or MUD.[43] Umbilical cord blood has become an acceptable alternative donor source in the absence of a MSD or MUD.[44,45]

Recent efforts utilizing targeted therapy, immunmodulators, or cellular approaches like donor lymphocyte infusion (DLI) aim to control or eradicate residual leukemic stem cells after allogeneic HSCT.[46] Depending on the individual risk of relapse and disease burden, these therapies are administered in a preemptive and therapeutic manner. They generally aim to enhance the graft-versus-leukemia (GVL) response while limiting the risk of acute or chronic graft-versus-host disease (GVHD). Chronic GVHD is the most significant cause of late, non-relapse mortality (NRM).[41]

- ***Myelodysplastic syndrome (MDS)***

HSCT is standard of care for close to all patients with pediatric MDS.[41] In patients with MDS-EB, a busulfan-based myeloablative preparative regimen is commonly applied. Most patients treated in Europe are given a preparative regimen with busulfan (targeted dose), cyclophosphamide and

melphalan.[38,41] Alternatively, busulfan, melphalan and fludarabine are administered.[47] Patients with a complex karyotype or *TP53* germline or somatic mutation have an inferior prognosis.[7,48]. At 5 years from transplantation, probability of event-free survival (EFS) is approximately 0.65, cumulative incidence of relapse (CIR) in the order of 0.2, and probability of non-relapse mortality (NRM) approximately 0.15.[38,49]

- ***Refractory cytopenia of childhood (RCC)***

For patients with RCC and presence of a chromosomal aberration, most commonly monosomy 7, the preparative regimen chosen is often less myeloablative than those applied for MDS-EB. It often consists of treosulfan, thiotepa and fludarabine.[41] Probability of survival following HSCT for MDS with an RCC histopathological pattern is in the order of 0.7.[49]

In patients with RCC and absence of markers of clonality, the bone marrow is often very hypocellular. Outcome of HSCT in these patients is favorable with a low relapse incidence and EFS at 5 years of approximately 0.9.[16,49] In cases with severely reduced marrow hematopoiesis, intensity of preparative regimens can be reduced e.g. with treosulfan and fludarabine.

- ***Myelodysplastic/myeloproliferative disorders (MDS/MPD) including juvenile myelomonocytic leukemia (JMML)***

Like in MDS-EB, preparative regimens prior to HSCT for MDS/MPD are generally myeloablative. For JMML, EWOG-MDS applies a regimen consisting of busulfan, cyclophosphamide and melphalan[39], while Japanese investigators employ the combination of busulfan, fludarabine, and melphalan.[42] A randomized study from the Childrens' Oncology Group in North America indicated that busulfan and fluarabine alone is inadequate to provide disease control for most patients with JMML.[50] EFS, CIR and NRM for patients transplanted for JMML are approximately 0.5, 0.35 and 0.15, respectively.[39,42] Lower risk patients have superior EFS due to a lower CIR. Disease recurrence remains the major cause of failure and occurs early within the first year from transplantation[51]. The CIR is reduced in the presence of grades II-III acute GVHD[44] or chronic GVHD[42,52], and withdrawal of immunosuppressive therapy in children with mixed chimerism can prevent subsequent occurrence of overt relapse.[53]

- ***Genetic conditions predisposing to MDS, RCC and MDS/MPD***

In the absence of MDS, RCC, MDS/MPD or another hematological diagnosis, HSCT is rarely indicated in individuals with a genetic predisposing condition.

1.3.3 Other Therapy Approaches

- ***Myelodysplastic syndrome (MDS)***

The role of intensive chemotherapy before HSCT for patients with MDS-EB has long been a matter of debate. In larger studies, there was no difference in EFS for patients who did or did not receive intensive chemotherapy before HSCT.[38] Currently, venetoclax-based therapies are frequently administered to bridge to HSCT.[54]

- ***Refractory cytopenia of childhood (RCC)***

In selected patients with RCC and a hypocellular bone marrow and normal karyotype, immunosuppressive therapy (IST) has been shown to be an effective treatment option.[4] However, patients treated with IST remain at risk of relapse and clonal evolution. As in studies on aplastic anemia, rabbit-ATG was less effective than horse-ATG.[4]

- ***Myelodysplastic/myeloproliferative disorders (MDS/MPD) including juvenile myelomonocytic leukemia (JMML)***

Based on a phase II study conducted in Europe[55], azacitidine (Vidaza®) was approved for therapy of newly diagnosed JMML by the US Food and Drug Administration (FDA) in 2022. Therapy responses to azacitidine were primarily noted in patients with lower risk of relapse.[55] Traditionally, low dose chemotherapy like 6-mercaptopurine, cytarabine or etoposide have been applied to bridge to HSCT[56]. In contrast to low dose chemotherapy, administration of high dose cytarabine and fludarabine can result in complete remission in some patients[57].

- ***Genetic conditions predisposing to MDS, RCC and MDS/MPD***

Like for other hematopoietic monogenic disorders, it is to be expected that gene therapy will become an option for some individuals with a genetic conditions predisposing to myeloid neoplasia.

2 Project Plan and Structure

2.1 Registry Design

The EWOG-MDS registry is an open international prospective multicenter registry that will collect clinical information on children and adolescents diagnosed with MDS, RCC, MDS/MPD or individuals with germline predisposition for these disorders. For this, data on diagnostic features including molecular genetics, treatments, and follow-up of individuals with pediatric MDS, RCC, MDS/MPD or genetic predisposition for these disorders cared for in one of the participating centers who have provided informed consent are reported to the National Coordinator and documented via electronic case report forms within a data management system and stored into one database.

2.2 Recruitment Period

Patients diagnosed with MDS, RCC, MDS/MPD or germline predisposition for these disorders after the initiation of the registry will be registered, and their data (initial and follow-up) will be continuously collected. Patients that have been diagnosed with one of these conditions before the initiation of the registry may retrospectively be registered after an agreement of the EWOG-MDS Coordinating Investigator and the respective National Coordinator (i.e. to fill the gap between closure of the previous registry and the initiation of the new registry). There is no predefined closure of the registry.

2.3 Patient Recruitment

Patients will be recruited at the participating center. These are departments of Pediatric Hematology and Oncology in Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Ireland, Israel, Italy, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and Switzerland.

The EWOG National Coordinators are responsible for confirming the diagnosis based on the respective results of the reference laboratories, confirming the eligibility and collecting the data.

3 Objectives and Data Collected

3.1 Objectives

- To prospectively and in selected situations retrospectively register all patients with newly diagnosed MDS, RCC, MDS/MPN or genetic predisposition for these disorders in all participating countries
- To study the epidemiology of MDS, RCC, MDS/MPN or genetic predisposition in childhood and adolescence
- To document the initial diagnostic work-up in reference laboratories
- To document clinical characteristics, treatment and outcome data (i.e. disease status, non-hematological phenotype, treatment decisions, treatment, health status, quality of live, survival)
- To assess biological disease features and correlate with clinical outcome data (prognostic and predictive markers)

3.2 Data collected

Data documented in the registry are collected during the routine clinical care of patients and usually reflect the standard of care for diagnosis and treatment.

- Demographic data
- Clinical symptoms
- Diagnostic features incl. morphological, histological, cytogenetic and molecular genetic studies
- Non-hematological phenotype
- Treatment decisions and applied therapy
- Health status, quality of life and outcome

3.3 Diagnostic Data of Reference Laboratories

It is the aim of the registry do document the high standard of the diagnostic work up performed in the national and international reference laboratories in the participating countries. Whenever available, data generated in the designated reference laboratories will be used to assess the inclusion criteria.

- Complete blood count including a full differential blood count and smears
- Fetal hemoglobin
- Bone marrow aspirate including a full differential count and smears
- Bone marrow biopsy
- Metaphase cytogenetics
- Fluorescence in Situ Hybridization (FISH) including at least chromosome 7 and 8 in the absence of metaphase cytogenetics
- Genetic testing for presence of germline and somatic mutations
- For patients with RCC: Exclusion of Fanconi anemia by DEB or MMC testing (growth arrest in flow cytometry or increase in chromosomal breakage)
- For patients with RCC: Exclusion of dyskeratosis congenita/telomere biology disorder by determination of telomere length by either quantitative polymerase chain reaction (qPCR) or Flow FISH (if accurate testing is available)

4 Subject Population

4.1 Inclusion Criteria

The population of the EWOG-MDS registry includes newly diagnosed patients with MDS, RCC, MDS/MPN and germline predisposition for these disorders. Patients will only be allowed to enter the registry if they and/or their caretakers provide written informed consent about their participation and if the physician has verified that the patient meets all of the inclusion criteria and none of the exclusion criteria.

- Confirmed clinical diagnosis of MDS, RCC, MDS/MPN, germline predisposition for these disorders
- Age < 21 years for patients with MDS, RCC, MDS/MPN; no age restriction for individuals with germline predisposition for MDS, RCC, MDS/MPN

4.2 Exclusion Criteria

Patients who do not fulfill the inclusion criteria or without legal capacity and or unable to understand the nature, significance and consequences of the registration in the registry may not be included.

- Severe aplastic anemia (SAA) registered in EWOG-SAA
- RCC in the classical IBMFSs Fanconi anemia, dyskeratosis congenita, severe congenital neutropenia, Shwachman-Diamond syndrome, Diamond-Blackfan anemia, and Pearson syndrome
- Transient myeloproliferative disorder in Down syndrome, myeloid neoplasms associated with Down syndrome
- Classical myeloproliferative neoplasm like chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, primary myelofibrosis, chronic eosinophilic leukemia

5 Procedures

Information about the EWOG-MDS registry and all essential documents are provided on the EWOG-MDS and EWOG-SAA homepage (www.ewog-saa-mds.org).

5.1 Patient Information and Informed Consent

If a patient is considered eligible for the EWOG-MDS registry, the treating physician will inform the patient or his/her legal representative about the registry and request their written informed consent. It is mandatory that written consent is obtained prior to any data transfer.

5.2 Patient Registration

After having confirmed the inclusion criteria, the treating physician enrolls the patient into the EWOG-MDS registry by registering the subject into the Data Base (MARVIN, Xclinical). The National Coordinator of the respective countries has access to the data and is responsible for the patient individual's eligibility. Once the eligibility is confirmed by the National Coordinator, each patient registered in the EWOG-MDS registry receives a consecutive patient identification number (EWOG identification number), which is given by the current CSC.

5.3 Data Collection

All patient's information and clinical follow-up will be collected from each participating center using a certified remote data entry electronical Case Report Form (eCRF) system (MARVIN, XClinical). In the participating centers the data are registered by an authorized person and are checked, dated and signed electronically by the treating physician. In addition, data can be entered and signed electronically by an authorized person in national reference labs. All registry related subject data will be captured in a pseudonymized form. The data base is validated and will be maintained according to respective standard operating procedures (SOPs).

Initial Data

The following data are collected in the database at diagnosis

- Demographic characteristics
- Disease characteristics
- Diagnostic work up

Follow-up Data

Data about treatment and outcome are collected in the data base. The data of follow-up is collected at least annually.

- Treatment
- Health status, quality of live and outcome

5.4 Registration of Patients Enrolled in Treatment Specific Clinical Trials

Patients participating in treatment specific clinical trials can also be registered in the EWOG-MDS registry. The participation in specific clinical treatment trials has to be documented in the registry. To avoid double entry of data, it`s desirable that data of patients participating in other clinical trials which are relevant to this registry, are exported from the respective study databases to the registry.

5.5 Discontinuation of a Registry Patient

The consent of a patient or the legal guardian can be withdrawn at any time without giving reason and without any disadvantages for further medical care. In case a patient or caretaker withdraws their consent, the treating physician has to inform the National Coordinator, which in turn informs the Coordinating Investigator of the EWOG-MDS registry. Once a patient has been discontinued from the registry, they can no longer be re-registered again. The date of discontinuation, all recorded results at this time and if known, the reasons for discontinuation are to be documented in the case report form (CRF).

6 Data Management

No onsite quality control and source data verification by a clinical monitor is performed in this registry. During the registry process, quality control of the documented data will be ensured through monitoring of the national data by the National Coordinator and central monitoring of the EWOG-MDS registry by the CSC. To achieve this, the data management at the national study center:

- Checks patient eligibility
- Monitors data entry and data quality
- Issues queries regarding completeness and plausibility of the data entries and supervises answering process
- Sends reminders to the treating physician and site personal for initial and follow up patient documentation

The data management at the CSC:

- Provides EWOG-MDS registry specific patient identification number
- Checks whether the eligibility of the patient is validated by a member of the steering committee i.e. the National Coordinator
- Monitors data entry and data quality
- Issues queries regarding completeness and plausibility of the data entries and supervises answering process
- Sends reminders to National Coordinators for initial and follow up of patient documentation

7 Statistical Analysis

A descriptive statistical analysis will be performed annually. It is the responsibility of the CSC to perform the statistical analysis and distribute the information to the National Coordinators.

The pre-specified analysis will include the following:

- Number of subjects enrolled in the registry compared to the number of expected cases per country.
- Demographics and baseline characteristics of the registered patients will be summarized overall, by country and in population sub-groups.
- Number and percentage of subjects with complete diagnostic work up as defined at the time of the registration.
- Clinical characteristics of the registered patients (e.g. the disease, comorbidities) will be summarized overall, by country and population sub-groups.
- Treatment characteristics (e.g. number of patients receiving a specific treatment protocol) will be summarized overall, by country and population sub-groups.
- Clinical outcomes (e.g. number of patients being cured or suffering from death related to the treatment or the disease) will be summarized overall, by country and population sub-groups.
- Lost to Follow-up: patients in whom no information is registered for >24 months will be considered lost to follow-up. The number and percentage of these patients will be summarized overall, by country and population sub-groups.

8 Biomaterial

The highest impact for the understanding of MDS, RCC, MDS/MPD or genetic predisposition syndromes underlying these disorders will be achieved if the results of the detailed clinical data collection within the registry are combined with the results of basic biological research performed in biomaterial of registered subjects. Therefore, biomaterials that have been collected during diagnostic procedures (such as blood, bone marrow, skin biopsies etc.) will be stored in qualified biobank. Samples that have not been used during diagnostic work up will be available for non-commercial

scientific investigations in MDS, RCC, MDS/MPN, germline conditions predisposing to these disorders, or acquired or congenital bone marrow failure disorders, or other rare hematopoietic malignancy in childhood and adolescence. Biomaterial will only be transferred to the biobank and be available for research if a) the subject and/or the caregiver have received adequate information and signed the respective consent and b) the research project has been approved by an independent ethics committee.

9 Ethical and Legal Principles

9.1 Subject Informed Consent Form (ICF)

Before enrollment in the EWOG-MDS registry, the patient and/or his legal representative will be informed that participation is voluntary and that he/she may withdraw at any time without giving reasons and without any effect on further medical care.

The patient will be given enough time and opportunity to obtain answers to any open questions. All questions should be answered to the satisfaction of the patient and/or his/her legal representatives. In addition, the patient will be given an information sheet, which contains all the important information in writing. Children and adolescents will receive appropriate information material for their age and should be asked for their assent whenever possible. The informed consent form (ICF) complies with regulatory requirements.

It is in the responsibility of the treating physician to obtain the patient's and/or his or her legal representatives' written consent before any data will be entered in the EWOG-MDS registry. For this purpose, the written consent form will be personally dated and signed by the patient and/or his or her legal representative and the physician conducting the informed consent discussion.

By signing the consent form, the patient agrees to participate voluntarily in the registry. After signing, the patient will be given one copy of the signed and dated written consent form and any other written information to be provided to the patients.

9.2 Ethical and Regulatory Requirements

This registry is based on the current version of the declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Prior to patient enrollment, the protocol, patient information sheet and the proposed ICF must be reviewed and approved by the Ethics Committee. Participating centers must have/apply for local ethics approval for the EWOG-MDS registry according to the applicable national/local regulatory requirements.

9.3 Data Protection and Confidentiality

Throughout this registry period, all data will be treated confidential and handled according to the national legal requirements.

Patients will be informed of the purpose and extent of the collection and use of personal data, particularly medical data. Findings obtained during the data collection of the registry and the respective analyses will be stored on electronic media and treated in strict confidence. For the protection of these data, organizational measures have been taken to prevent disclosure to unauthorized third parties. For example, the patient data will be captured in pseudonymized form (unique patient identification code) throughout the documentation and evaluation phase.

Patient data are only accessible to specialists for scientific research and are used only for purpose of scientific research. The identity of patients will be kept confidential in any kind of publication. As medical data information are essential for conducting biological research studies, patients will be informed that the registry data are linked to the data base of collected biosamples.

9.4 Insurance

As an international prospective registry, the EWOG-MDS registry is not a clinical study. The inclusion criteria are based on a standardized diagnostic approach reflecting the standard of care and the treatment is independent of the participation in the registry.

9.5 Archiving

After completion of the registry, all essential documents will be retained at the CSC in accordance with national regulations. The National Coordinator will be responsible for the storage of data at a national level. Originals of all documentation and copies of outgoing correspondence concerning the registry will be stored and retained in a safe area at the CSC in Freiburg and Ulm.

10 Publication

10.1 Public Disclosure and Information Platform

In order to better achieve the aims outlined above, a disease specific information platform will be introduced (www.ewog-saa-mds.org). With the help of this platform, updated information on standard-of-care diagnostic procedures, available treatment guidelines and research projects will be detailed for professionals, patients and the public.

The EWOG-MDS registry will be also made public in national and international clinical trial registries (i.e. Deutsches Register Klinischer Studien (www.drks.de)).

10.2 Publication of Results

Any formal presentation or publication of data collected within the registry will be considered as a joint publication by the participating parties. It requires the agreement of the EWOG-MDS Coordinating Investigator and all National Coordinators. Authorship will be determined by mutual agreement and based on contribution.

Results generated from registry data may be presented during scientific symposia or published in a scientific journal only after review and written approval by all National Coordinators and the Coordinating Investigator.

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Appendix 1: National Responsibilities in Germany (country)

National Coordinator	**Prof. Dr. Miriam Erlacher** Department of Pediatrics and Adolescent Medicine Ulm University Medical Center Eythstraße 24, 89075 Ulm, Germany Tel: (+49) 0731 500 57001 E-mail: miriam.erlacher@uniklinik-ulm.de
Deputy	**PD Dr. Brigitte Strahm** Division of Pediatric Hematology and Oncology Department of Pediatrics and Adolescent Medicine University of Freiburg Breisacher Straße 62, 79106 Freiburg Tel.: (+49) 0761 270 43963 E-mail: brigitte.strahm@uniklinik-freiburg.de

Reference Laboratories (status of October 2025)

Cytomorphology	**PD Dr. Ayami Yoshimi** Division of Pediatric Hematology and Oncology Department of Pediatrics and Adolescent Medicine University of Freiburg Breisacher Straße 62, 79106 Freiburg **Dr. Ingrid Furlan** Department of Pediatrics and Adolescent Medicine Ulm University Medical Center Eythstraße 24, 89075 Ulm, Germany
Pathology	**Prof. Dr. Stephan Schwarz-Furlan** Institute of Pathology Kaufbeuren-Ravensburg Supra-regional association for histology and cytology Dr.-Gutermann-Straße 6 87600 Kaufbeuren **Prof. Dr. Martina Rudelius** Department of Pathology, University Hospital, LMU Thalkirchner Straße 36 80337 München
Cytogenetics	**Dr. rer. nat. Thea Reinkens** Department of Human Genetics Hannover Medical School Carl Neuberg-Str.1 30625 Hannover
Fanconi Anemia	**Dr. Reinhard Kalb** Department of Human Genetics Biocenter, Würzburg Medical School Am Hubland 97074 Würzburg

Appendix 2: Coordinating Study Center (CSC) (status of October 2025)

Site Ulm
Dr. Ingrid Furlan
Department of Pediatrics and Adolescent Medicine
Ulm University Medical Center
Eythstraße 24,
89075 Ulm, Germany

Tel: (+49) 0731 500 56823
E-mail: ingrid.furlan@uniklinik-ulm.de

Site Freiburg
PD Dr. Brigitte Strahm
Division of Pediatric Hematology and Oncology
Department of Pediatrics and Adolescent Medicine
University of Freiburg
Breisacher Straße 62,
79106 Freiburg

Tel.: (+49) 0761 270 43645, Fax -96 46200
E-Mail: brigitte.strahm@uniklinik-freiburg.de

Project Management

Olga Istomina
Division of Pediatric Hematology and Oncology
Department of Pediatrics and Adolescent Medicine
University of Freiburg
Breisacher Straße 62, D-79106 Freiburg, Germany

Tel.: (+49) 0761 270-43452
E-mail: ewog-mds-saa@uniklinik-freiburg.de

Axel Gebert
Division of Pediatric Hematology and Oncology
Department of Pediatrics and Adolescent Medicine
University of Freiburg
Breisacher Straße 62, D-79106 Freiburg, Germany

Tel.: (+49) 0761 270-43952
E-mail: ewog-mds-saa@uniklinik-freiburg.de

Maria Zernickel
Department of Pediatrics and Adolescent Medicine
Ulm University Medical Center
Eythstraße 24,
89075 Ulm, Germany

Tel: (+49) 0731 500 57145
E-mail: maria.zernickel@uniklinik-ulm.de

Patrycja Schlingeloff
Department of Pediatrics and Adolescent Medicine
Ulm University Medical Center
Eythstraße 24,
89075 Ulm, Germany
Tel: (+49) 0731 500 57076
E-mail: patrycja.schlingeloff@uniklinik-ulm.de

Statistics	Peter Nöllke, MPH Division of Pediatric Hematology and Oncology Department of Pediatrics and Adolescent Medicine University of Freiburg Breisacher Straße 62, D-79106 Freiburg, Germany Tel.: (+49) 0761/270 43453 E-mail: ewog-mds-saa@uniklinik-freiburg.de
Data Management	Anne Breier Division of Pediatric Hematology and Oncology Department of Pediatrics and Adolescent Medicine University of Freiburg Breisacher Straße 62, D-79106 Freiburg, Germany Tel.: (+49) 0761/270 43946 E-mail: ewog-mds-saa@uniklinik-freiburg.de Elena Huber Division of Pediatric Hematology and Oncology Department of Pediatrics and Adolescent Medicine University of Freiburg Breisacher Straße 62, D-79106 Freiburg, Germany Tel.: (+49) 0761/270 43639 E-mail: ewog-mds-saa@uniklinik-freiburg.de

Appendix 3: List of National Coordinators of EWOG-MDS (status of November 2025)

Michael Dworzak, MD St. Anna Children's Hospital and Cancer Research Institute Kinderspitalgasse 6 1090 Wien, Austria	Riccardo Masetti, MD University of Bologna Sant'Orsola-Malpighi Hospital Paediatric Oncology and Haematology Via Albertoni 15 40138 Bologna, Italy
Barbara De Moerloose, MD Ghent University Hospital, 5K6 Dept. of Pediatric Hematology-Oncology De Pintelaan 185 9000 Ghent, Belgium	Jochen Buechner, MD Oslo University Hospital Department of Pediatric Hematology and Oncology 0424 Norway
Martina Sukova, MD University Hospital Motol Dept. of Pediatric Hematology / Oncology Vúvalu 84 150 06 Prague 5, Czech Republic	Marek Ussowicz, MD Wroclaw Medical University Department of Pediatric Hematology/Oncology Ul. Borowska 213 50-556 Wroklaw, Poland
Henrik Hasle, MD Aarhus University Hospital Skejby Department of Pediatrics 8200 Aarhus N, Denmark	Paula Kjollerstrom, MD Hospital Dona Estefânia Centro Hospitalar Lisboa Central R. Jacinta Marto 1169-045 Lisbon, Portugal
Kirsi Jahnukainen, MD Helsinki University Central Hospital Children`s Hospital/ Division of Hematology-Oncology and Stem Cell Transplantation 00029 Helsinki, Finland	Marko Kavcic, MD University Children´s Hospital of Ljubljana Department of Pediatric Hematology and Oncology Bohoričeva 20, 1000, Slovenia
Miriam Erlacher, MD/PhD Department of Pediatrics and Adolescent Medicine Ulm University Medical Center Eythstraße 24, D-89075 Ulm, Germany Tel: (+49) 0731 500 57001 E-mail: miriam.erlacher@uniklinik-ulm.de	Ivana Bodova, MD National Institute of Children's Diseases Faculty of Medicine, Comenius University Haematology and Transfusiology Dpt. Limbová 1, 83340 Bratislava, Slovakia
Sophia Polychronopoulou, MD Aghia Sophia Children's Hospital Department of Pediatric Hematology-Oncology Thivon & M.Asias, 11525 Athens, Greece	Albert Catala, MD Hospital Sant Joan de Déu Servei d'Hematologia Passeug Sant Joan De Deu 2 8950 Barcelona, Spain
Krisztián Kállay, MD United St. István and St. László Hospital Pediatric Hematology and Stem Cell Transplantation Unit Gyáli 5-7t, H-1097 Budapest, Hungary	Markus Schmugge, MD University Children's Hospital Department of Pediatric Hematology/Oncology Steinwiesstr.75 8032 Zürich, Switzerland
Andrea Malone, MD Our Lady´s Hospital for Sick Children Dept. of Pediatric Hematology & Oncology Crumlin, Dublin 12, Ireland	Valerie de Haas, MD Princess Maxima Center for Pediatric Oncology Diagnostic Laboratory / DCOG Laboratory Heidelberglaan 25 3584 CS Utrecht, The Netherlands
Shlomit Barzilai-Birenboim, MD Schneider Children´s Medical Center of Israel Dept. of Pediatric Hematology.Oncology 14 Kaplan St. 49202 Petah-Tikva, Israel	Dominik Turkiewicz, MD Skåne University Hospital Department of Pediatric Oncology/Hematology Trollebergsvägen 5 221 85 Lund,Sweden