

## Guideline for the Management of Adult Myelodysplastic Syndromes

### Version History

Version	Date	Summary of Change\Process
0.1	12.10.09	Draft developed by Dr Juliet Mills (JM). Presented at Haematology NSSG.
0.2	14.10.09	Reformatted by Lara Barnish (LB) for comment and approval by JM.
0.3	17.10.09	With comments from JM.
0.4	09.10.09	Presented at the Clinical Governance Sub-Group. Minor formatting changes recommended. For consultation with Andrew Stanley (AS) and review by JM.
0.5	16.03.10	With changes from JM and approved by AS
0.5	07.05.10	To Haematology NSSG for final comment
1.0	21.05.10	Final Version with AS comments included. Resubmitted to the guidelines subgroup.
1.1	28.04.11	With amendment by Juliet Mills for re-approval by the Clinical Governance Committee.
2.0	10.05.11	Endorsed by the Governance Committee

<b>Date Approved by Network Governance</b>	<b>May 2011</b>
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<b>Date for Review</b>	<b>May 2014</b>
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### **Changes between version 1 and version 2**

*The removal of an age description of 70 years from section 6.1.2 a.*

#### **1. Scope of the Guideline**

This guidance has been produced to support the following:

- The management of patients suspected of having a myelodysplastic syndrome
- The management of patients diagnosed with a myelodysplastic syndrome

#### **2. Guideline Background**

2.1 This document aims to combine up to date research, current thinking, and local expert opinion to generate Network Guidelines.

2.2 In Pan Birmingham Cancer Network two hospitals are designated transplant centres for haematological malignancies - University Hospital Birmingham Foundation Trust and Heartlands Hospital (part of Heart of England Foundation Trust). These two hospitals treat patients with

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haematological malignancies at BCSH levels 1-4. In addition to this Good Hope Hospital (part of Heart of England Foundation Trust) practises to level 1 and Worcester Royal Hospital (part of Worcestershire Acute Hospitals Trust), and Sandwell and West Birmingham Hospitals NHS Trust, Sandwell site practise to level 2.

- 2.3 These guidelines support the BCSH Guidelines for the Diagnosis and Therapy of Adult Myelodysplastic Syndromes (2003)<sup>1</sup>. These guidelines will be reviewed following the publication of future BCSH guidance.

### **3. Evaluation of Suspected Myelodysplastic Syndrome (MDS)**

#### **3.1 History should be taken including:**

- a) Symptoms of anaemia, recurrent infections, bleeding/bruising
- b) Prior exposure to chemotherapy/radiation
- c) Family history of MDS/Acute Myeloid Leukaemia

#### **3.2 Physical examination should include:**

- a) Pallor/infection/bruising
- b) Splenomegaly

#### **3.3 Initial investigations should take place as follows:**

- a) Full blood count and blood film (cytopenia(s), red cell macrocytosis, dysplastic features)
- b) Assay of serum ferritin, vitamin B12 and folate levels

#### **3.4 Reactive causes of dysplasia should be excluded. These include:**

- a) Megaloblastic anaemia
- b) Human immunodeficiency virus infection
- c) Alcoholism
- d) Recent cytotoxic therapy
- e) Severe intercurrent illness

### **4. Further Investigation and Diagnosis**

The diagnosis and classification of MDS remain dependent on the morphological examination of blood and bone marrow cells. Diagnostic criteria should ideally distinguish MDS from reactive conditions causing dysplastic haematopoiesis and from other clonal myeloid disorders. These criteria include the following.

#### **4.1 Bone Marrow Aspirate**

A bone marrow aspirate is necessary to make a confident diagnosis of MDS and to provide important information regarding disease classification and prognosis. This test may not, however, be necessary in elderly patients in whom a definitive diagnosis of MDS would not alter management or whose poor general health precludes active treatment.

#### **4.2 Bone Marrow Trepine**

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Bone marrow histology complements the morphological information obtained from a marrow aspirate and hence a trephine biopsy should be performed in all cases of suspected MDS where bone marrow examination is indicated. The assessment of cellularity and fibrosis define morphological variants, with the identification of hypocellular MDS of particular therapeutic importance<sup>2</sup>.

#### 4.3 **Cytogenetic Analysis of Bone Marrow**

A chromosomal abnormality confirms the presence of a clonal disorder aiding the distinction between MDS and reactive causes of dysplasia. In addition it provides major prognostic value. Cytogenetic analysis should therefore be performed in all patients for whom bone marrow examination is indicated.

#### 4.4 **Immunophenotypic Analysis of Bone Marrow**

Immunophenotyping of bone marrow is recommended and can be useful in determining the percentage of marrow blasts, particularly when myeloid dysplasia makes morphological enumeration difficult. The marrow blast percentage is necessary for disease classification and prognostication.

#### 4.5 **Morphological Diagnostic Criteria for MDS**

Minimal diagnostic criteria are not clearly defined in MDS and the diagnosis of MDS is susceptible to inter-observer variation. Difficulties also arise because a variety of reactive disorders are associated with dysplastic morphology and mild dysplastic features are frequently seen in the marrow of healthy people with normal blood counts<sup>3</sup>.

In order to increase the reliability of diagnosing MDS, the following recommendations are made:

- a) Where possible at least 200 marrow cells and 20 megakaryocytes should be evaluated.
- b) Dysplastic features should be present in at least 10% marrow cells
- c) The presence of pseudo-pelger neutrophils, ring sideroblasts, micromegakaryocytes and increased blasts correlate most strongly with the presence of clonal markers in MDS and show least inter-observer variation.
- d) It is recommended that a diagnosis of MDS is not based on the presence of neutrophil hypogranularity alone, due to the fact that neutrophil granularity is critically dependent on optimal staining.

If morphological diagnosis remains uncertain, it is recommended that the patient be monitored with repeat morphological assessment at appropriate intervals.

#### 4.6 **Hypocellular MDS Versus Aplastic Anaemia**

The diagnosis of hypocellular MDS is of importance, as preliminary data suggest that the response to immunosuppressive therapy is higher than in cases of MDS with normo or hypercellular marrows<sup>4</sup>. The diagnosis of myelodysplasia requires the presence of dysplastic features in megakaryocytes and/or myeloid cells or an excess of blasts. Erythroid dysplasia is found in aplastic anaemia and cannot be used alone to

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distinguish MDS from AA. The presence of an abnormal karyotype strongly favours the diagnosis of MDS, but cases of aplastic anaemia with an abnormal karyotype, without morphological features of MDS, and with a low risk of transformation to MDS or AML, have been described.

## **5. Disease Classification**

Patients with MDS are classified according to the WHO classification system<sup>5</sup> (Table 1) and assigned a prognostic score according to the International Prognostic Scoring System (IPSS)<sup>6</sup> (Table 2).

**Table 1:****WHO Classification and Criteria for the Myelodysplastic Syndromes**

<b>Disease</b>	<b>Blood findings</b>	<b>Bone marrow findings</b>
Refractory anaemia (RA)	Anaemia No or rare blasts	Erythroid dysplasia <5% blasts <15% ringed sideroblasts
Refractory anaemia with ringed sideroblasts (RARS)	Anaemia No blasts	Erythroid dysplasia only ≥15% ringed <5 % blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods <1 x 10 <sup>9</sup> /l monocytes	Dysplasia in ≥ 10% of cells myeloid cell lines <5% blasts in marrow No Auer rods <15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods <1 x 10 <sup>9</sup> /L monocytes	Dysplasia in ≥ 10% of cells in 2/more myeloid cell lines ≥15% ringed sideroblasts <5% blasts No Auer rods
Refractory anaemia with excess blasts – 1 (RAEB-1)	Cytopenias <5 blasts No Auer rods <1 x 10 <sup>9</sup> /L monocytes	Unilineage or multilineage dysplasia 5% to 9% blasts No Auer rods
Refractory anaemia with excess blasts – 2 (RAEB-2)	Cytopenias 5% to 19% blasts Auer rods ± <1 x 10 <sup>9</sup> /L monocytes	Unilineage or multilineage dysplasia 10% to 19% blasts Auer rods ±
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias No or rare blasts No Auer rods	Unilineage dysplasia in granulocytes or megakaryocytes <5% blasts No Auer rods
MDS associated with isolated megakaryocytes del (5q)	Anaemia <5% blasts Platelets normal or Increased	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts No Auer rods Isolated del (5q)

**Table 2:**

**International Prognostic Scoring System: Derivation of Patient Score (IPSS)**

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

Karyotype: Good risk, normal, -Y, del(5q), del(20q)

Poor risk, complex (≥3 abnormalities) or chromosome 7 anomalies

Intermediate risk, other abnormalities.

Cytopenias defined as haemoglobin concentration <10 g/dl, neutrophils <1.8 ×10<sup>9</sup>/l and platelets <100 ×10<sup>9</sup>/l.

Scores for risk groups are as follows: Low, 0; Intermediate-1, 0.5-1.0; Intermediate-2, 1.5-2.0; and High, 2.5

**Table 3:**

**WHO Classification of Myelodysplastic/Myeloproliferative diseases.**

<ul style="list-style-type: none"> <li>• <b>Chronic Myelomonocytic Leukaemia (CMML)</b></li> <li>• <b>Atypical Chronic Myelomonocytic Leukaemia</b></li> <li>• <b>Juvenile myelomonocytic leukaemia</b></li> </ul>
<p><b>Chronic Myelomonocytic Leukaemia (CMML)</b></p> <ul style="list-style-type: none"> <li>• Persistent peripheral blood monocytosis &gt;1x10<sup>9</sup>/l</li> <li>• No Philadelphia chromosome or BCR/ABL fusion gene</li> <li>• &lt;20% blasts in the blood or bone marrow – includes myeloblasts, monoblasts and promonocytes</li> <li>• Dysplasia in one or more myeloid lineage</li> </ul>
<p>If dysplasia is absent or minimal the diagnosis of CMML may still be made if the other requirements are present and an acquired clonal cytogenetic abnormality is present in the marrow cells or the monocytosis has been persistent for at least 3 months and all other causes of monocytosis have been excluded.</p> <p>Diagnose <b>CMML-1</b> when &lt;5% blasts in blood and &lt;10% in bone marrow.            Diagnose <b>CMML-2</b> when blasts 5-19% in blood, or 10-19% in marrow or if Auer rods are present and blasts are &lt;20% in blood or marrow.            Diagnose CMML-1 or CMML-2 with eosinophilia when the above criteria are present and when the eosinophilia in the peripheral blood is &gt;1.5x10<sup>9</sup>/l.</p>

## 6. Management of Myelodysplastic Syndromes

All patients should be discussed at the Trust Haematology MDT meeting. Decisions should be based on the IPSS score (Appendix 2) taken during a stable clinical phase<sup>7</sup>.

Eligibility for entry into open trials should be considered – (See section 9). Patients who may be eligible for allogeneic transplantation should be discussed with/referred to a local level 4 Transplant Unit (University Hospital Birmingham NHS Foundation Trust or Heart of England NHS Foundation Trust).

### 6.1 Supportive Care

Supportive care remains the most important aspect of management for patients with good prognosis MDS and those with poor prognosis disease in whom age or performance status precludes them from receiving more intensive forms of therapy. The aim is to reduce morbidity and mortality while providing an acceptable quality of life.

#### 6.1.1 **Red Cell Transfusion**

The use of red cell transfusions should be considered in any patient with symptoms of anaemia. Blood transfusions should be administered according to local Trust transfusion policies.

#### 6.1.2 **Iron Chelation**

The clinical importance of iron overload in MDS patients is difficult to assess and remains unclear. Similarly, the role of iron chelation therapy, in terms of patient suitability and specific benefit, has yet to be identified.

Based on consensus guidelines and statements for the treatment of iron overload in patients with MDS<sup>8,9</sup>, patients who satisfy the following criteria could be considered for iron chelation therapy:

- a) Transfusion-dependent patients with low-risk (IPSS low or Int-1) MDS, for whom the predicted survival is greater than 4 years. Iron chelation therapy should be commenced when the patient has received approximately 25 units of red cells and when the serum ferritin is > 1000ng/ml or where there is alternative evidence of iron overload.
- b) First-line therapy is usually with subcutaneous desferrioxamine. The oral iron chelators, deferasirox and deferiprone, may be considered in patients who demonstrate intolerance or lack of response.

#### 6.1.3 **5q- Syndrome**

Lenalidomide is not currently licensed for use in this group of patients and applications for use would need to be made locally on an individual patient basis.



#### 6.1.4 **Erythropoietin, GCSF and Immunosuppressive Therapy**

Patients with symptomatic anaemia may be suitable for treatment with erythropoietin, GCSF or immunosuppressive therapy depending on disease subtype, marrow cellularity serum erythropoietin level and transfusion requirements (see Appendix 1).

### 6.2 Intensive Chemotherapy / Stem Cell Transplantation

6.2.1 All patients eligible for intensive chemotherapy/stem cell transplantation (SCT) should be discussed with a local Transplant Unit (University Hospital Birmingham NHS Foundation Trust or Heart of England NHS Trust)

#### 6.2.2 **IPSS Low**

Neither intensive chemotherapy nor stem cell transplantation can be recommended for this group whose median survival without treatment is

4.8

(>60yrs) -11.8(<60yrs)

#### 6.2.3 **IPSS Int-1 and Int-2/High**

See flow charts (See Appendix 2 and 3).

#### 6.2.4 **Chemotherapy alone in Int-2/High risk MDS**

Patients ineligible for SCT should be considered for intensive AML type chemotherapy.

### 6.3 Azacytidine in Int-2/High Risk MDS

The final appraisal determination issued by the National Institute for Health and Clinical Excellence (NICE) includes guidance that azacytidine is not recommended as a treatment option for patients with intermediate-2 and high-risk MDS according to the International Prognostic Scoring System (IPSS). Clinicians may still wish to make an individual patient request to the patients PCT if they believe them to be outside of the NICE appraisal.

### 6.4 Supportive care/investigational therapy:

Patients who do not fall into any of the above categories, or who are ineligible for such therapy, should be offered supportive care or investigational therapies within clinical research protocols.

## 7. **Patient Information and Counselling**

7.1 All patients, and with their consent, their partners will be given access to appropriate written information during their investigation and treatment, and on diagnosis will be given the opportunity to discuss their management with a clinical nurse specialist who is a member of the relevant MDT. The patient should have a method of access to the haematology team at all times. Useful advice can be obtained from: [www.ukmdsforum.org](http://www.ukmdsforum.org)

7.2 Access to psychological counselling will be available if required.



## 8. Palliative Care

Palliative care services will be made available to all patients as deemed appropriate by the MDT.

## 9. Clinical Trials

9.1 Wherever possible, patients who are eligible should be offered the opportunity to participate in National Institute for Health Research portfolio clinical trials and other well designed studies.

9.2 Where a study is only open at one Trust in the Network, patients should be referred for trial entry. A list of studies available at each Trust is available from Pan Birmingham Cancer Research Network. Email: [PBCRN@westmidlands.nhs.uk](mailto:PBCRN@westmidlands.nhs.uk)

9.3 Patients who have been recruited into a clinical trial will be followed up as defined in the protocol.

## Monitoring of the Guideline

Implementation of the guidance will be considered as a topic for audit by the NSSG in 2013.

## Author

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## References

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6. Greenberg et al. Blood,1997;89:2079-88.
7. Malcovati et al. JCO,2005;23:7594-7603.
8. Gattermann. Leuk Res,2007.
9. Bennett. Am J Hemat,2008;83(11)858-61.
10. NICE guidance on azacytidine due for publication onto to NICE Website March 2010

**Approval Date of Network Site Specific Group**      Date      February 2011

**Approval Date by the Clinical Governance Team**      Date      May 2011

**Approval Signatures**

**Pan Birmingham Cancer Network Governance Committee**

Name:      Doug Wulff



Signature      Date      May 2011

**Pan Birmingham Cancer Network Manager**

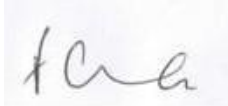
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Signature      Date      May 2011

**Network Site Specific Group Clinical Chair**

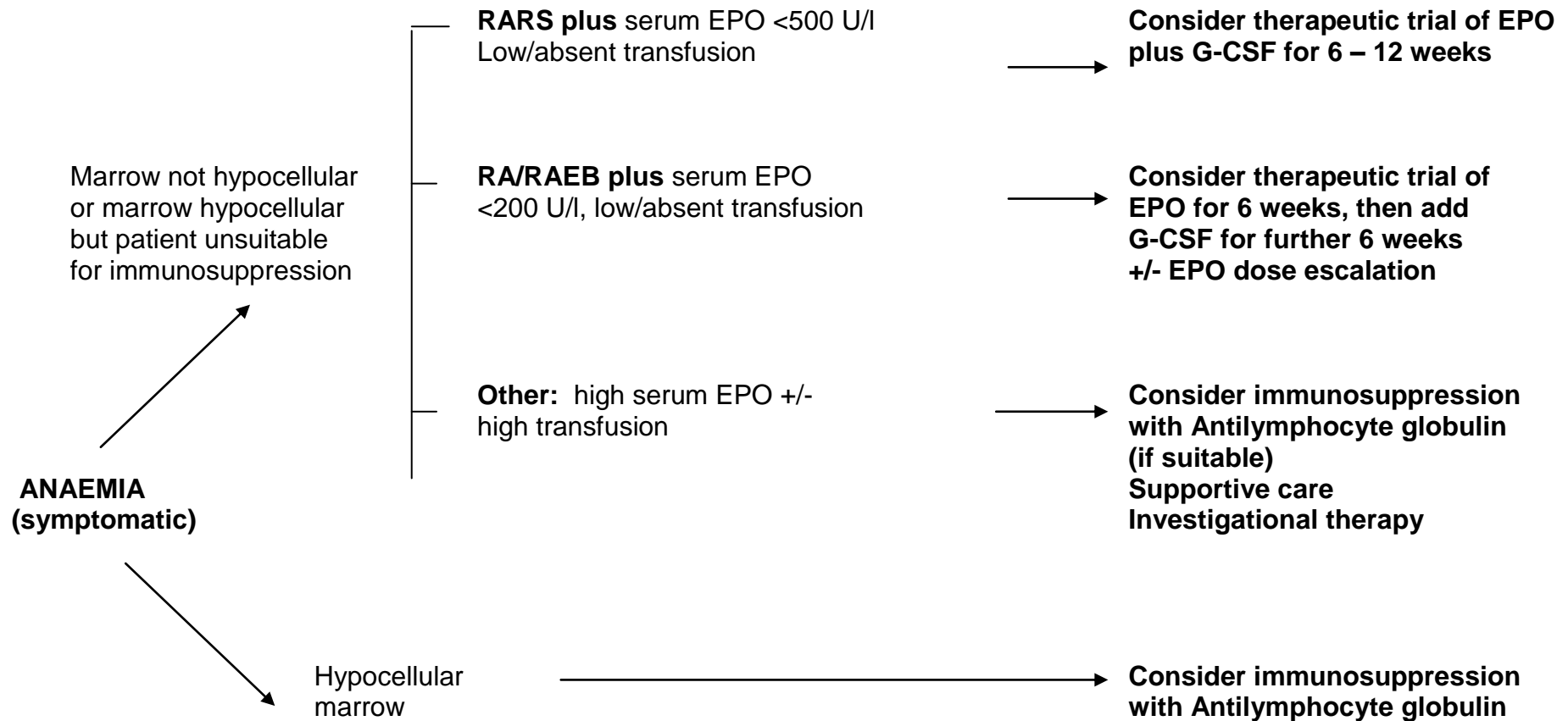
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Signature      Date      May 2011

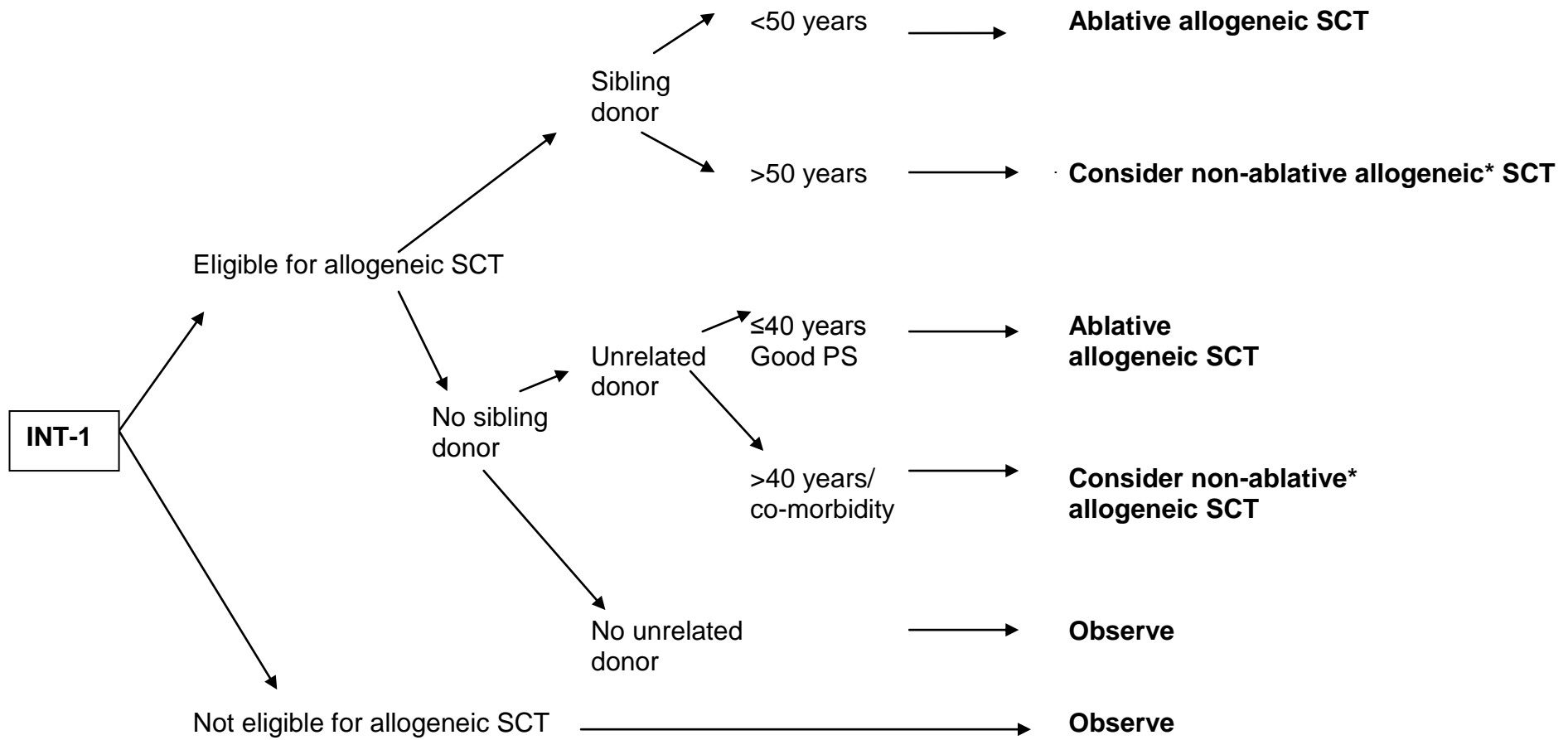
**ENDORSED BY THE GOVERNANCE COMMITTEE**

**Erythropoietin, G-CSF and Immunosuppressive Therapy: Management of Symptomatic Anaemia in MDS**



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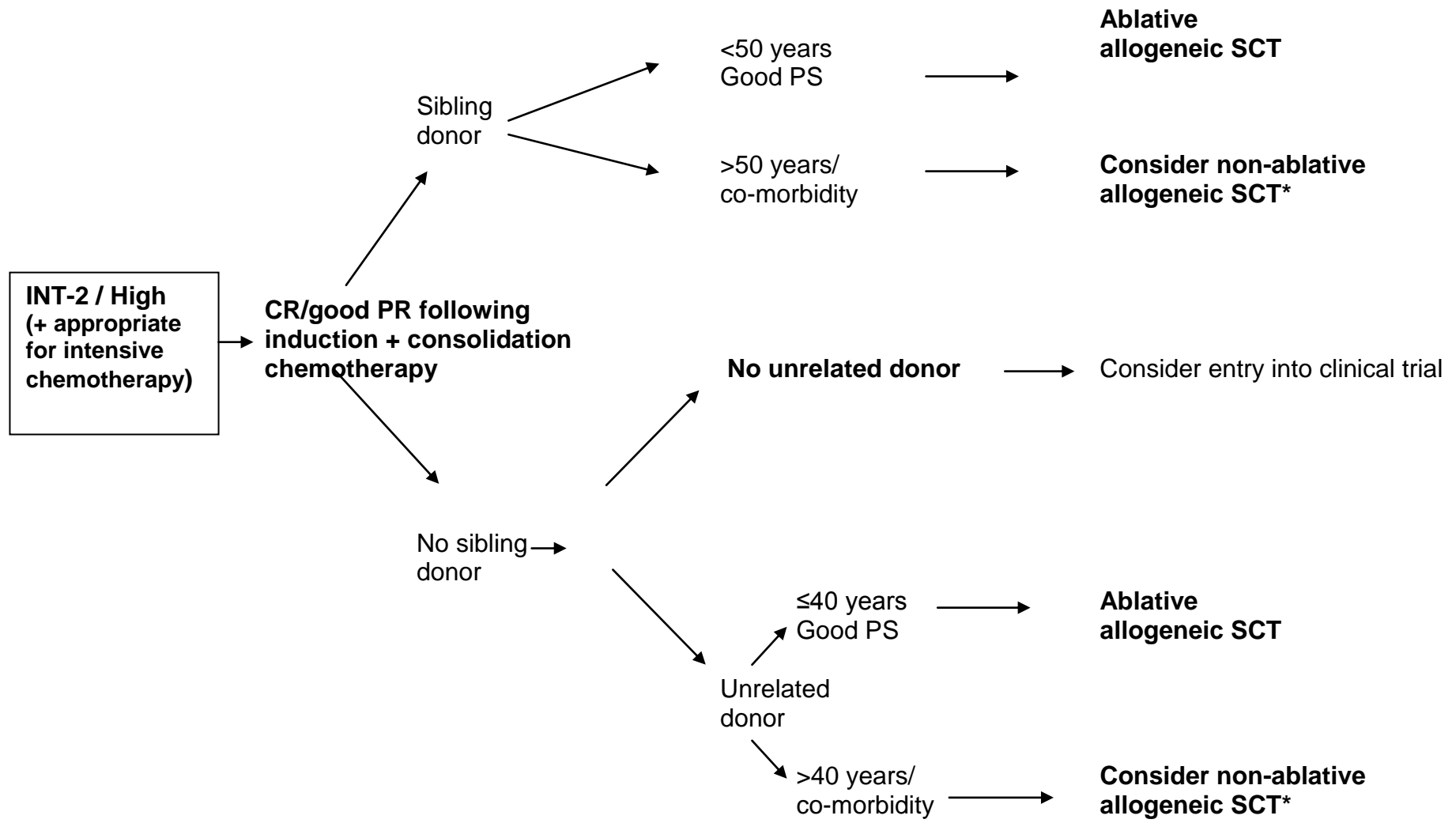
**Algorithm for the Management of IPSS Int-1 risk MDS patients**



\* Within CRP where available

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**Algorithm for the Management of IPSS Int-2/High risk MDS patients**



\*Within CRP where available

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