RM Partners
West London Cancer Alliance
Hosted by The Royal Marsden NHS Foundation Trust

SELCA
South East London Cancer Alliance

NHS
North Central and East London Cancer Alliance

Pan-London Haemato-Oncology Clinical Guidelines

Acute Leukaemias and Myeloid Neoplasms
Part 4: Myeloproliferative Neoplasms

January 2020

Contents

Lead authors 2020:

Professor Claire Harrison, Guy's and St Thomas' NHS Foundation Trust

Dr Mallika Sekhar, Royal Free London NHS Foundation Trust and University College London Hospitals NHS Foundation Trust

Dr Christopher Mitchell, North Middlesex University NHS Foundation Trust

Dr Donal McLornan, Guy's and St Thomas' NHS Foundation Trust and University College London Hospitals NHS Foundation Trust

2018 Edition;

Professor Claire Harrison, Guy's and St Thomas' NHS Foundation Trust

Dr Mallika Sekhar, Royal Free London NHS Foundation Trust and University College London Hospitals NHS Foundation Trust

Disclaimer

These guidelines should be read in conjunction with the latest NICE guidance, and all applicable national/international guidance. The prescribing information in these guidelines is for health professionals only. It is not intended to replace consultation with the Haematology Consultant at the patient's specialist centre. For information on cautions, contra-indications and side effects, refer to the up-to-date prescribing information. While great care has been taken to see that the information in these guidelines is accurate, the user is advised to check the doses and regimens carefully and if there is any uncertainty about the guidance provided, you should discuss your queries with a Haematology Consultant or Senior Pharmacist. No set of guidelines can cover all variations required for specific patient circumstances. It is the responsibility of the healthcare practitioners using them to adapt them for safe use within their institutions and for the individual needs of patients.

Contact us

The writing cycle for the guidelines will be from May-July each year. If you wish to be part of the writing group, please contact us through the following link: Pan London Blood Cancer (or via uclh.panlondonbloodcancer@nhs.net).

If you wish to report errors or omissions that require urgent attention please contact us via the same email addresses.

1 Introduction

Myeloproliferative neoplasms (MPN) include essential thrombocythaemia (ET), polycythaemia vera (PV) and primary myelofibrosis (PMF). They are all closely related and have an intrinsic tendency to evolve into acute myeloid leukaemia (AML), confirming their classification as haemato-oncological disorders. They are characterised by an increased incidence of thrombosis in the region 20 -30% over 15 years, and premature death for the majority of patients. MPNs are perhaps the orphan diseases of haemato-oncology, but these patients, if managed judiciously, have prolonged survival, with a median survival greater than 10–15 years for ET and PV. However, available treatments have significant side-effect profiles and need to be chosen with care, particularly in young patients. The last decade has seen the publication of a considerable body of clinical data informing clinical decisions. Many therapeutic options, however, remain unlicensed. The following sections contain current management protocols for ET, PV and MF (including MF in patients with an antecedent history of ET and PV and pre-fibrotic MF).

Other entities within the MPN group – MPNU, chronic eosinophilia, chronic neutrophilic leukaemia and mast cell disorders – are not covered in these guidelines. These conditions listed in the World Health Organization (WHO) criteria for MPN 2016 (WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC, Lyon 2016) are:

Myeloproliferative neoplasms

- Chronic myeloid leukemia (CML), BCR-ABL1^{+}
- Chronic neutrophilic leukemia (CNL)
- Polycythemia vera (PV)
- Primary myelofibrosis (PMF)
  - PMF, prefibrotic/early stage
  - PMF, overt fibrotic stage
- Essential thrombocythemia (ET)
- Chronic eosinophilic leukemia, not otherwise specified (NOS)
- MPN, unclassifiable
- Mastocytosis

Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of

- PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2
- Myeloid/lymphoid neoplasms with PDGFRA rearrangement
- Myeloid/lymphoid neoplasms with PDGFRB rearrangement
- Myeloid/lymphoid neoplasms with FGFR1 rearrangement
- Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

- Chronic myelomonocytic leukemia (CMML)
- Atypical chronic myeloid leukemia (aCML), BCR-ABL1-
- Juvenile myelomonocytic leukemia (JMML)
- MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
- MDS/MPN, unclassifiable

2 Clinical Features

2.1 Essential thrombocythaemia (ET)

ET is characterised by a persistent thrombocytosis. The previously accepted platelet count threshold >600 x 10^9/L has been revised to >450 x 10^9/L. Short-term complications of ET include thrombosis and, less frequently, haemorrhage. In common with PV, long-term problems include a risk of transformation to MF and acute leukaemia, although these are less frequent in ET.

Thrombotic events affect the arterial and venous macro and microvasculature, as well as the placental circulation. Microvascular events predominate in ET typically causing erythromelalgia (asymmetric erythema, congestion and burning pain in the hands and feet), which may progress to ischaemia and gangrene, migraine-like headaches and transient ischaemic attacks (TIAs).

Approximately 30–50% of patients are symptomatic at presentation.

2.2 Polycythaemia vera (PV)

PV is characterised by an erythrocytosis (packed cell volume (PCV) >0.52 in men and >0.48 in women, WHO 2008, BSH 2019 criteria; >49% in men and >48% in women, WHO 2016 criteria) and sometimes thrombocytosis and neutrophilia according to the BCSH. Recent WHO and BSH criteria are shown below. The median age at presentation is 55–60 years.

Vascular thromboses, especially arterial events and more rarely bleeding, are major events over the patient's lifetime. In the longer term (10–15 years), MF or 'spent phase' may occur and up to 5-10% of patients may develop AML.

Aquagenic pruritus, gout and splenomegaly are also classical clinical features, but only occur in a few patients.

2.3 Primary myelofibrosis (PMF) including Prefibrotic-MF (Pre-MF)

Chronic idiopathic myelofibrosis, or PMF may arise *de novo* or as a late phase of ET, and particularly PV known as post-PV (PPV)-MF and post-ET (PET)-MF respectively. Fibrosis is thought to arise from an interaction between clonal megakaryocytes, releasing mitogens such as platelet-derived growth factor (PDGF) and transforming growth factor that directly increase fibroblast proliferation.

PMF has a median age of presentation of 50–60 years. Symptoms relate to bone marrow failure (anaemia, infection, bleeding) or progressive splenomegaly and a pro-inflammatory state (pain, weight loss, sweating). Progression to acute leukaemia occurs in up to 25% of patients (more than PV or ET) and may occasionally be associated with extramedullary collections of myeloid progenitors (chloromas).

Pre-fibrotic MF (Pre-MF) is a relatively recently described entity. Akin to ET, pre-MF is characterised by a chronic thrombocytosis, but it differs from ET in terms of bone marrow morphology and prognosis (Thiele, *et al*., 2011). The bone marrow in pre-MF is markedly hypercellular, with pronounced granulocytic hyperplasia, erythroid hypoplasia, and distinctive megakaryocytic morphology, distinguishing it from ET. However, there is no significant increase in reticulin fibres in pre-MF, distinguishing it from PMF. The life expectancy in pre-MF is probably intermediate between ET and PMF, but the natural history of pre-MF is unknown and studies are on-going. This is something we could usefully contribute to across London, i.e. defining natural history and outcome.

3 Referral Pathways

Patients with a high WBC, haemoglobin/haematocrit or platelet count and/or suspected MPN by other features (e.g. splenomegaly, unprovoked and unusual site for a thrombotic episode) should be referred to a haematologist for assessment.

All new patients should be referred to the MDT for confirmation of diagnosis, prognosis and management plan, taking into account their performance status, needs and co-morbidities. A joint approach with elderly care physicians and palliative care teams may be appropriate, depending on the performance status of the patient and the phase of disease.

The following patients should be referred to the MDT:

- All new patients with MPN in order to confirm the diagnosis and treatment plan
- All patients where a new line of therapy needs to be considered
- All patients with a restaging assessment
- All patients in whom an allogeneic stem cell transplant is a consideration.

Information to be ideally captured and documented prior to, or during, the MDT includes:

- Demographic information
- Referring physician and/or GP
- Performance status
- An indicator of co-morbidities (e.g. co-morbidity score)
- Any relevant history
- Pertinent positive and negative findings on physical examination (splenomegaly, rashes, etc.)
- Spleen size (by ultrasound)
- FBC, haematinics, LFTs, U&E, LDH, urate, reticulocyte count, serum erythropoietin (for cases of erythrocytosis), transfusion dependency
- Bone marrow aspirate and trephine histology (where available)
- Bone marrow aspirate immunophenotyping, if relevant
- Cytogenetic status, if relevant
- Mutational status (in most cases this will include the driver mutations JAK2/CALR (subtype where available)/MPL but in patients with atypical features, so-called ‘triple negative’ MF and patients where SCT is considered a wider mutational panel should be considered where available as this will aid prognostication).
- Specific diagnosis/category of MPN and prognostic risk score (we recommend recording which diagnostic criteria were used, i.e. WHO or BCSH)
- Other relevant imaging
- Availability of a clinical trial/research study and whether the patient is eligible
- Management and treatment plan
- Key worker/clinical nurse specialist
- Named consultant or team (as per local work patterns).

Patients with PV, ET and MF may be managed at facilities with at least BSCH Level 1 designation. Complex patients may be referred to centres with specific expertise or which have suitable and available trials (examples of such patients include, though are not limited to, those displaying therapy intolerance/ failure, unusual site thromboses such as splanchnic vein thromboses or for complex or higher risk pregnancies). Patients who are being considered for an allogeneic stem cell transplant should be referred to a JACIE-accredited centre. All patients with MF eligible for a transplant option should be referred for a transplant opinion, ideally early in the pathway to facilitate donor identification. This is dependent upon local practice.

3.1 Children

Children below the age of 16 years with a diagnosis of MPN must be referred to the paediatric oncology team at the principal treatment centre (PTC) and must not be managed exclusively by adult site-specific teams. However adult input in this specialty which is extremely rare in the paediatric setting is critical.

- The joint PTC for children aged below 16 years for South Thames is The Royal Marsden (Sutton)/St George's Hospital.
- The PTC for North Thames (including North West London) is Great Ormond Street Hospital/ University College London Hospitals.
- All patients <1 year from both North and South Thames should be referred to Great Ormond Street Hospital.

3.2 Teenagers and young adults

Teenagers aged 16–18 should be managed at a PTC for teenage and young adult (TYA) cancers. Young adults aged 19–24 should be given the choice of being managed at a PTC or TYA-designated hospital.

- The PTC for TYA for South Thames is The Royal Marsden (Sutton)/Guy's Hospital
- The PTC for North Thames (including North West London) is University College London Hospitals.

All patients within this age range, regardless of place of care, should be referred to the TYA MDT at the relevant PTC.

4 Investigation and Diagnosis

A thorough clinical history and examination should be performed, focusing upon exclusion of secondary causes.

For patients with unprovoked blood clots (in particular of the splanchnic or cerebral venous circulation, or other unusual sites), check JAK2 and CALR + MPL mutational status even if blood counts are normal.

Diagnostic criteria: in this document we present both BCSH and WHO diagnostic criteria; we recommend consistent use of one of these options.

4.1 Essential thrombocythaemia (ET)

There is no diagnostic hallmark for ET. The diagnosis is made by excluding other MPNs, and a reactive or secondary thrombocytosis. Causes of a reactive thrombocytosis include iron deficiency anaemia, chronic inflammation (e.g. rheumatoid arthritis, inflammatory bowel disease), splenectomy, acute haemorrhage, and malignant disease. In an otherwise well patient, the diagnosis is generally uncomplicated. However, where conditions co-exist which may cause a reactive thrombocytosis, this may make the diagnosis more difficult.

Historically, the diagnostic criteria for ET were those of the polycythaemia vera study group. Forty years on, continual development of the diagnostic criteria for MPNs set the stage for the World Health Organization (WHO) Diagnostic Criteria 2001, modified in 2008 and again in 2016. The revised WHO criteria (2016) require characteristic bone marrow morphology, a platelet threshold of 450 x 10^9/L and molecular analysis for the JAK2 V617F mutation and other clonal markers. Modified BCSH (British Committee for Standards in Haematology, 2013) criteria or WHO criteria may be used.

4.1.1 WHO ET criteria (2016)

Major criteria

1. Platelet count ≥450 x 10^9/L

2. BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibres

3. Not meeting WHO criteria for BCR-ABL11 CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms

4. Presence of JAK2, CALR, or MPL mutation.

Minor criterion

Presence of a clonal marker or absence of evidence for reactive thrombocytosis.

Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion.

4.1.2 BCSH (2013) diagnostic criteria for ET

Diagnosis requires A1–A3 or A1 + A3–A5

A1 Sustained platelet count >450 x 10^9/L

A2 Presence of an acquired pathogenetic mutation (e.g. in JAK2, CALR or MPL genes)

A3 No other myeloid malignancy, especially PV*, PMF†, CML‡ or MDS§

A4 No reactive cause for thrombocytosis and normal iron stores

A5 Bone marrow aspirate and trephine biopsy showing increased megakaryocyte numbers displaying a spectrum of morphology with predominant large megakaryocytes with hyperlobated nuclei and abundant cytoplasm. Reticulin is generally not increased (grades 0–2/4 or grade 0/3)

* Excluded by a normal haematocrit in an iron-replete patient.

† Indicated by presence of significant bone marrow fibrosis (greater or equal to 2/3 or 3/4 reticulin) AND palpable splenomegaly, blood film abnormalities (circulating progenitors, tear-drop cells) or unexplained anaemia (Barosi, *et al.*, 1999; Mesa, *et al.*, 2007).

‡ Chronic myeloid leukaemia; excluded by absence of BCR-ABL1 fusion from bone marrow or peripheral blood.

§ Myelodysplastic syndrome; excluded by absence of dysplasia on examination of blood film and bone marrow aspirate.

Investigations to be performed on all patients include:

- FBC and blood film
- Haematinics
- Renal/liver profiles and CRP
- ANA and RhF
- Chest X-ray (most patients, all smokers).

Where there is a high index of suspicion on first appointment, otherwise at second visit:

- JAK2 V617F, CALR (with subtype) and MPL W515L/K screen
- Abdominal ultrasound scan
- Bone marrow aspirate and trephine (BMAT), cytogenetics in all patients <60 years, JAK2/MPL/CALR mutation negative patients and patients where there is a suspicion of MDS, pre-MF or MF, regardless of mutation status
- PB/BM samples sent for *BCR-ABL* FISH to exclude a diagnosis of CML, especially if atypical features.
- Consider testing for vWFAg and Ricof looking for acquired VWD in patients with platelets >1000 x 10^9/L and haemorrhagic symptoms

The decision to proceed to formal cytogenetic analysis on any sample received is made at the diagnostic multidisciplinary (MDT) meeting.

The recent WHO criteria (2016) for ET place greater emphasis upon bone marrow histology, in particular megakaryocyte morphology, and also emphasis is placed on discriminating both PV and prefibrotic MF from JAK2 positive ET. The other condition that must be excluded when diagnosing ET is myelodysplastic syndrome. This is usually associated with a low rather than high platelet

count and is characterised by dysplastic features morphologically and particular chromosomal abnormalities. Note that some patients with refractory anaemia with ring sideroblasts (RARS) or chromosome 5 abnormalities and MDS may also carry the JAK2 V617F mutation (see WHO classification for MDS-RARS-T).

4.2 Polycythaemia vera (PV)

An erythrocytosis is defined as an HCT >0.52 in men and >0.48 in women (*per* BCSH, 2007, 2019), although the WHO (2016) have a lower HCT threshold (0.49 for men; 0.47 for women) this has not yet been widely adopted. The JAK2 V617F mutation negative erythrocytosis cases may still be a PV case without a genetic marker or with a JAK2 exon12 mutation; alternatives include a pseudo/apparent, primary congenital, secondary congenital or acquired, or idiopathic erythrocytosis, all of which require definition. Diagnostic criteria for JAK2 wild type PV are listed below.

Table 1: WHO (2016) diagnosis of PV

Diagnosis needs both major and one minor criteria OR major criterion no.1 with two minor criteria (after exclusion of secondary causes):

Major	1. Hb >16.5 g/dL in men; >16.0 g/dL in women or hematocrit >49% in men; >48% in women or increased red cell mass (RCM)* 2. BM biopsy† showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size) 3. Presence of JAK2V617F or JAK2 exon 12 mutation
Minor	Subnormal serum erythropoietin level

Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion†.

*More than 25% above mean normal predicted value.

†Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: Hb >18.5 g/dL in men (haematocrit> 55.5%) or >16.5 g/dL in women (haematocrit > 49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF).

The current BSH 2018 erythrocytosis guideline (McMullin et al, 2019) suggests a three-stage approach to investigation, this is practically helpful in the wider context of erythrocytosis. The procedure outlined below is an adaptation of this guidance, based upon modified diagnostic criteria suggested by Campbell and Green (2006), simplifying the diagnosis and the need for investigation in JAK2-positive PV. Determination of a case of JAK2-negative PV or an alternative cause of erythrocytosis will require further investigation.

JAK2-positive PV (Diagnosis requires both to be present)	
A1	PCV >0.52 men, >0.48 in women or a raised RCM (>25% above predicted)
A2	Mutation in JAK2
JAK2-negative PV (Diagnosis requires A1 + A2 + A3 + either another A or two B criteria)	
A1	Raised Red Cell Mass (>25% above predicted) or a PCV >0.60 in men, >0.56 in women
A2	Absence of mutation in JAK2
A3	No cause of secondary erythrocytosis
A4	BM histology consistent with polycythaemia vera
A5	Palpable splenomegaly
A6	Presence of acquired genetic mutation (excluding BCR-ABL) in haemopoietic cells
B1	Thrombocytosis: platelet count >450 x 10^9/L
B2	Neutrophil leucocytosis (N>10x109/l in non-smokers and > or equal to 12.5 x 109/l in smokers)
B3	Radiological evidence of splenomegaly
B4	Low serum erythropoietin

The primary clinical assessment of an erythrocytosis case should include a thorough history and examination seeking out possible secondary causes, followed by Stage 1 investigations to confirm or refute a diagnosis of a JAK2 V617F-positive PV. The majority of patients (excluding borderline erythrocytosis) and all ex- and current smokers will require a chest X-ray. Urinalysis is a simple effective screen for renal disease, which should be performed in all patients at the initial visit. Patients may present with co-morbidities; thus, regardless of a diagnosis of PV, a review of potential secondary causes is pertinent. Additional investigation of possible secondary causes will vary according to symptoms or signs present.

Erythrocytosis Stage 1 Investigations:

- FBC and blood film
- Renal and Liver Function tests
- Serum Calcium levels
- Serum ferritin levels
- JAK2 V617F mutational analysis
- Chest X-ray (smokers or otherwise indicated)
- Urinalysis
- Serum erythropoietin level
- Pulse oximetry and venous carboxyhaemoglobin

If the initial screening tests are negative for a *JAK2* mutation and there is no obvious secondary cause, further investigations are indicated. A Red Cell Mass (RCM) may be required to define whether a case is a pseudo/apparent or an absolute erythrocytosis at this point and should be discussed with the Haematology consultant. Of particular note, a RCM is not interpretable if a venesection has been performed. A PCV of >0.60 and >0.56 in a man or woman, respectively, can be assumed to have an absolute erythrocytosis and a RCM would not be indicated. Cases

confirmed as an absolute erythrocytosis require remaining Stage 2 tests, as appropriate, with consultant guidance.

*Erythrocytosis Stage 2/3: (**see Flow chart 1**)*

- Abdominal ultrasound (may be moved earlier)
- RCM performed in nuclear medicine – discuss with consultant if appropriate. As per BSH guidelines this may be helpful to confirm an absolute erythrocytosis versus an apparent erythrocytosis. Patients with Hct >0·60 (males) or >0·56 (females) can be assumed to have an absolute erythrocytosis. Access to this test is variable nationally as is accepted in the current BSH guidelines.
- Haemoglobinopathy screen

Further testing is based upon the serum EPO level measured during stage 1 investigations

Normal or low serum EPO levels

- JAK2 exon 12 mutational analysis
- Bone Marrow Histology can aid diagnosis of PV from secondary erythrocytosis

High Serum EPO levels

- Consider further investigation for secondary cause if clinically suspected (referral to respiratory/ renal or sleep studies as required)
- Consider Lung function tests as required dependent on clinical phenotype
- CT or MRI imaging head and neck (cerebellar haemangioblastoma/ meningioma/ parathyroid adenoma or carcinoma)

For cases of both low/normal and high serum EPO - consider indications for further genetic testing (see below) if no diagnosis is yet revealed:

- Red cell directed NGS panels (including VHL, PHD and erythropoietin receptor mutations (EPOR) and EGLN1) where available for detection of acquired genetic abnormalities
- Of note this has some limitations as some mutations are non-specific
- P50 testing is labour intensive and not readily available but may be considered where required (n.b may not be required if red cell panel is performed which include HbA and HbB)

The serum erythropoietin level, JAK2 exon12 mutation screen and abdominal ultrasound can aid the diagnosis of JAK2 V617F-negative PV. Ultimately a bone marrow biopsy is critical ideally before cytotoxics are commenced.
Hypoxaemia causing a secondary erythrocytosis can be screened for by assessing oxygen saturation using pulse oximetry (92% is the arbitrary cut-off for significance) and the carboxyhaemoglobin level available from biochemistry. It is important to subtract the carboxyhaemoglobin level from the oxygen saturation to obtain the correct estimate of oxygen saturation.
Abdominal ultrasound can also exclude secondary causes of erythrocytosis, particularly renal and hepatic pathology, including hepatocellular carcinoma. The abdominal ultrasound combined with urinalysis and GFR estimation enables a renal disease screen.

A BMAT should be performed in all cases of JAK2 V617F-negative absolute erythrocytosis where no cause of secondary erythrocytosis is found. The presence of typical histology will support a diagnosis of JAK2-negative PV, whereas its absence will suggest an alternative cause. A baseline BMAT should also be considered in all JAK2 V617F-positive patients who are under 60 for future reference regarding progression, although it is not essential to confirm a diagnosis. A BMA sample should be sent for cytogenetics – the decision whether to formally proceed to assess these samples is made in the diagnostic MDT meeting.

For those patients where the aetiology of absolute erythrocytosis is still undefined. Stage 3, consisting of further specialised investigations, needs to be considered and discussed with a consultant. Symptoms, including snoring, daytime somnolence and a body habitus suggestive of sleep apnoea, may warrant referral for sleep studies. The Epworth score is a useful indicator for referring for sleep studies. A red cell panel genetic screen including the erythropoietin receptor mutation, HIF-1alpha and proline dehydroxylase mutations amongst others can be sent to the local lab with facilities for red cell gene panel analysis e.g. the haematology lab at Viapath at King's College Hospital, and may lead to a diagnosis of a primary congenital erythrocytosis. A p50 estimation/beta chain sequencing (via red cell NGS) may demonstrate a high affinity haemoglobin causing a secondary congenital erythrocytosis. As mentioned previously a p50 is increasingly replaced by a red cell panel has been performed as this screens for haemoglobin variations.

4.3 Prefibrotic myelofibrosis (pre-MF) and primary myelofibrosis (PMF)

For diagnosis of PMF, exclude other MPNs (PV, ET and CML) and disorders in which marrow fibrosis can develop as a secondary feature (e.g. metastatic carcinoma, lymphoma, irradiation, TB and leishmaniasis).

The following are generally necessary to confirm PMF:

- Splenomegaly
- Increased BM fibrosis. In later stages, new osteoid bone is formed (osteomyelofibrosis)
- Leucoerythroblastic blood film
- Absence of other MPN, including CML (perform FISH for bcr-abl)
- Exclude secondary causes of myelofibrosis (see above)
- It is useful to obtain an LDH level and cytogenetics (consider from peripheral blood) periodically to monitor
- In patients with atypical features, so called ‘triple negative’ MF and patients where SCT is considered a wider mutational panel should be considered where available.

The following tests should be performed:

- FBC and blood film, blast count
- Haematinics
- Renal, liver profile, LDH and urate level
- JAK2 V617F, CALR (subtype) and MPL W515L/K screen
- Chest X-ray
- Abdominal ultrasound scan
- BMAT with samples sent for cytogenetics and FISH for bcr-abl.

Table 2: WHO diagnostic criteria of pre-MF: need to meet all three major and at least one minor criterion

Major	1. Megakaryocytic proliferation and atypia, without reticulin fibrosis grade 1*, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis 2. Not meeting the WHO criteria for BCR-ABL11 CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms 3. Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker,† or absence of minor reactive BM reticulin fibrosis‡
Minor	Presence of at least 1 of the following, confirmed in 2 consecutive determinations: a. Anaemia not attributed to a comorbid condition b. Leukocytosis ≥11 x 10^9/L c. Palpable splenomegaly d. LDH increased to above upper normal limit of institutional reference range

Diagnosis of pre MF requires meeting all 3 major criteria, and at least 1 minor criterion.

*See Table 5.

†In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1) are of help in determining the clonal nature of the disease.

‡Minor (grade 1) reticulin fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukaemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

Table 3: WHO overt PMF criteria

Major	1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3* 2. Not meeting WHO criteria for ET, PV, BCR-ABL11 CML, myelodysplastic syndromes, or other myeloid neoplasms 3. Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker,† or absence of reactive myelofibrosis‡
Minor	Presence of at least 1 of the following, confirmed in 2 consecutive determinations: a. Anemia not attributed to a comorbid condition b. Leukocytosis ≥11 x 10^9/L c. Palpable splenomegaly d. LDH increased to above upper normal limit of institutional reference range e. Leukoerythroblastosis

Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion

*See Table 5.

†In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1) are of help in determining the clonal nature of the disease.

‡BM fibrosis secondary to infection, autoimmune disorder, or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

Table 4: BCSH diagnostic criteria

BCSH diagnostic criteria (2015) for PMF: requires A1 + A2 and any two B criteria

A1	Bone marrow fibrosis ≥ 3 (on 0–4 scale)
A2	Pathogenetic mutation (e.g. in JAK2, CALR or MPL), or absence of both BCR-ABL1 and reactive causes of bone marrow fibrosis
B1	Palpable splenomegaly
B2	Unexplained anaemia
B3	Leucoerythroblastic blood film
B4	Tear-drop red cells
B5	Constitutional symptoms[1]
B6	Histological evidence of extramedullary haematopoiesis.

BCSH diagnostic criteria for post-PV and post-ET MF: requires A1 + A2 and any two B criteria

A1	Bone marrow fibrosis ≥ 3 (on 0–4 scale)
A2	Previous diagnosis of ET or PV
B1	New palpable splenomegaly or increase in spleen size of ≥ 5cm
B2	Unexplained anaemia with 2g/dL decrease from baseline haemoglobin
B3	Leucoerythroblastic blood film
B4	Tear-drop red cells
B5	Constitutional symptoms*
B6	Histological evidence of extramedullary haematopoiesis.

* Drenching night sweats, weight loss >10% over 6 months, unexplained fever (>37.5^{0}C) or diffuse bone pains.

Table 5: Grading of myelofibrosis

Myelofibrosis grading	
MF-0	Scattered linear reticulin with no intersections (crossovers) corresponding to normal BM
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibres mostly consistent with collagen, and/or focal osteosclerosis*
MF-3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibres consistent with collagen, usually associated with osteosclerosis*

Semiquantitative grading of BM fibrosis (MF) with minor modifications concerning collagen and osteosclerosis. Fibre density should be assessed only in hematopoietic areas.

* In grades MF-2 or MF-3 an additional trichrome stain is recommended.

Source: Arber, *et al*. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127:2391–2405

4.4 Pathology

> *Careful attention must be paid to the labelling of forms and samples before sending to the Specialist Integrated Haematological Malignancy Diagnostic Service (SIHMDS). Samples are unlikely to be processed unless clearly and correctly labelled.*

BMAT:

- Slides for morphology to SIHMDS lab
- 2–5ml in EDTA for immunophenotyping with a slide
- 2–5ml in EDTA for molecular genetics
- 2–5ml in heparin (PFH or lithium heparin) for cytogenetics/FISH
- Trephine for histopathology

4.5 Imaging

All patients should have an ultrasound of the abdomen performed at diagnosis to document spleen (and liver) size, and thereafter when clinically appropriate.

5 Risk Stratification

We recommend that all patients be risk stratified at diagnosis and yearly thereafter.

Risk stratification systems for ET and PV: please choose a system and stay with it.

Table 6: Risk stratification systems in MPN for vascular/thrombotic events

MPN Risk group	**BCSH ET**	**IPSET ET**	**BSH PV**	
Low	Age <40 years No high-risk features	0	Age <65 and no past h/o PV associated thrombosis	
Intermediate	Age 40-60 years No high-risk features	1-2	CV risk factors, high WBC, extreme thrombocytosis, Hct uncontrolled with v/section	
High	Any feature from list below	≥3	Age >65 and/or past h/o PV associated arterial or venous thrombosis	
	IPSET: Age ≥60 = 1; CV risk factors = 1; Previous thrombosis = 2; Jak2V617F = 2 – (pain, early satiety) splenomegaly. NB this may be an indication for treatment rather than a risk factor *per se** * These risk factors are more controversial and have not been fully agreed. ***A number of variables including age, prior thrombosis, the presence of splenomegaly, serum lactate dehydrogenase (LDH) level, degree of reticulin staining, presence of an abnormal karyotype and JAK 2 mutant allele burden may be utilised when counselling the patient on longer term prognosis including overall survival and disease transformation risk.*** ***Deep sequencing for 'high risk mutations' e.g. ASXL1, SRSF2, IDH1/2 is not yet 'standard of care' but may be considered in selected cases where their presence may influence management.***			

5.1 Primary myelofibrosis (PMF)

The most widely adopted risk stratification was validated on 1,500 PMF patients: the International Prognostic Scoring System IPSS (Cervantes, 2008). But this applies to patients at diagnosis only. Subsequent studies have shown that the high-risk features of the IPSS can be applied in a dynamic manner to give useful prognostic information during follow-up of MF patients (DIPSS,

Passamonti, 2010). A more recent scoring system is the DIPSS-Plus (Gangat, 2011), which takes into account transfusion dependence and thrombocytopenia. Even more recently The MIPSS-70/MIPSS-70 plus (http://www.mipss70score.it), the Grinfeld or personalised prognostic score (https://jg738.shinyapps.io/mpn_app/_w_b33c5c1f/) and the MYSEC (for PPV and PET MF) scores (http://www.mysec-pm.eu) have been introduced these are available via websites.

Only the MYSEC score has been validated for post-ET or post-PV MF (Passamonti, *et al* 2017)

Variable	**IPSS**	**DIPSS**
Age >65 years	√	√
Constitutional symptoms	√	√
Haemoglobin <10g/dL	√	√
Leukocyte count >25 x 10^9/L	√	√
Circulating blasts ≥1%	√	√
	1 point each	**1 point each but Hb=2**

DIPSS-plus add one to the DIPSS score for each of:		
Platelet count <100 x 10^9/L		
RBC transfusion need		
Unfavourable karyotype +8,-7/7q-,i(17q),inv(3), -5/5q-,12p-, 11q23 rearr.		

MYSEC Score for PET- and PPV-MF is available via online calculators and includes weighted points of age at diagnosis of PET or PPV-MF, Haemoglobin <11g.dL, platelets <150 x10^9/L, circulating blasts ≥3% blasts, CALR-unmutated genotype, constitutional symptoms (Passamonti, et al 2017).

Linking Scores to Prognosis

	IPSS	DIPSS	DIPSS-Plus	MIPSS70	MIPSS70-Plus	GIPSS	MPN Personalised Risk Calculator
Criteria	- Age >65y (1) - Hb <100 g/L (1) - WCC >25 x10^9/L (1) - PB blasts ≥ 1% (1) - Constitutional Sx (1)	- Age >65y (1) - Hb <100 g/L (2) - WCC >25 x10^9/L (1) - PB blasts ≥ 1% (1) - Constitutional Sx (1)	- Age >65y (1) - Hb <100 g/L (1) - WCC >25 x10^9/L (1) - PB blasts ≥ 1% (1) - Constitutional Sx (1) - Unfavourable Karyotype[a] (1) - Transfusion dependency (1) - Platelets < 100 x10^9/L (1)	- Hb <100 g/L (1) - WCC > 25 x10^9/L (2) - PB blasts ≥ 2% (1) - Constitutional Sx (1) - Platelets < 100 x10^9/L (2) - Absence of *CALR* type 1/like mutations (1) - HMR category (1) - ≥2 HMR mutations (2) - BM fibrosis grade ≥2 (1)	- Hb <100 g/L (1) - PB blasts ≥ 2% (1) - Constitutional Sx (1) - Unfavourable karyotype (3) - Absence of *CALR* type 1/like mutations (2) - HMR category (1) - ≥2 HMR mutations (2)	- Age >60y (2) - Very high-risk karyotype (3) - High-risk karyotype (1) - *JAK2* (2) - *MPL* (2) - *CALR type 2* (2) - *ASXL1/SRSF2* (1) - Triple negative (2)	- Age at diagnosis - Hb - WCC - Platelet count - Gender - Prior Thrombosis - Splenomegaly - *JAK2 V617F* - *MPL* - *CALR* - *JAK2 Exon 12* - Other mutations/cytogenetic anomalies[a]
Available online web-links		http://www.siematologia.it/LG/DIPSS/DIPSS.htm	https://qxmd.com/calculate/calculator_315/dipss-plus-score-for-prognosis-in-myelofibrosis	http://www.mipss70score.it/	http://www.mipss70score.it/		https://cancer.sanger.ac.uk/mpn-multistage/
Risk groups, scores (OS)							
- Low	0 (11.3y)	0	0 (185m)	0-1 (27.7y)	0-2 (20y)	0	N/A as risk personalised and not grouped
- Int-1	1 (7.9y)	1-2 (14.2y)	1 (78m)	2-4 (7.1y)	3 (6.3y)	1-2 (9y)	
- Int-2	2 (4y)	3-4 (4y)	2-3 (35m)			2-3 (5y)	
- High	≥3 (2.3y)	≥5 (1.5y)	≥4 (16m)	≥5 (1.9y)	4-6 (3.9y)	≥5 (2.2y)	
- Very High					≥7 (1.7y)		

IPSS – International Prognostic Scoring System; DIPSS – Dynamic international prognostic scoring system; MIPSS – Mutation enhanced international prognostic scoring system; GIPSS – Genetic inspired prognostic scoring system; y – years; Hb – Haemoglobin; WCC – white cell count; PB – peripheral blood; Sx – symptoms; m - months; HMR - high molecular risk

a - Other mutations and cytogenetic anomalies included - *ASXL1, TET2, SRSF2, TP53, DNMT3A, EZH2, U2AF1, SF3B1, CBL, NF1, IDH2, PPM1D, NFE2, ZRSR2, NRAS, GNAS, SH2B3, KRAS, PTPN11, CUX1, SETBP1, KIT, BCOR, IDH1, RUNX1, GATA2, PHF6, FLT3, MLL3, GNB1, STAG2, MBD1*

9pUPD, Tri 9, 1pUPD, 1q+, 4qUPD, 5q-, 7q-, Tri 8, 11q-, 12pUPD, 13qUPD, 14qUPD, 17p, 18qUPD, 19pUPD, 20q-

6 Patient Information/Support

All patients must have access to a key worker. This is usually (but not always) the clinical nurse specialist.

The clinical nurse specialist/key worker should be present at diagnosis and at any significant discussion where treatment changes and outcomes are discussed. In the absence of the clinical nurse specialist, a senior nurse may deputise who must ensure that all conversations are documented in the patient's notes and on the electronic patient record. Where it is not possible for the clinical nurse specialist or a deputy to be present, patients should be given the clinical nurse specialist's contact numbers. The clinician leading the consultation should advise the clinical nurse specialist who should then arrange to make contact with the patient.

The clinical nurse specialist should ensure that all patients are offered a Holistic Needs Assessment (HNA) at key pathway points, including within 31 days of diagnosis; at the end of each treatment regime; and whenever a person requests one. Following each HNA, every patient should be offered a written care plan. This plan should be developed with the patient and communicated to all appropriate healthcare and allied healthcare professionals.

Written and verbal information is essential and the key worker/clinical nurse specialist plays a key role in ensuring that patients have access to appropriate and relevant written information about their condition.

Information booklets are available to download from the Bloodwise, Macmillan Cancer Support, and MPN Voice websites:

www.bloodwise.org.uk/info-support/myeloproliferative-neoplasms

www.macmillan.org.uk/Cancerinformation/Cancerinformation.aspx

www.mpnvoice.org.uk

7 Treatment

Formal written consent should be obtained for all patients before commencing any cytoreductive therapy (red cell-, white cell- or platelet-controlling drugs) including hydroxyurea (hydroxycarbamide/HU), anagrelide, interferon-alpha, ruxolitinib, busulfan or radioactive phosphorus.

- MPN related symptoms can have a major impact upon the quality of life of MPN patients and these should be documented formally and regularly reviewed using a validated tool such as the MPN- symptom assessment form (MPN-SAF) or MPN10.
- Cardiovascular risk factors should also be identified, discussed and regularly reviewed with all MPN patients. The GP should be informed to undertake regular CV risk assessment.

7.1 Essential thrombocythaemia (ET)

7.1.1 Management and prognosis

Patients with ET, akin to those with PV, are predisposed to thrombosis, which is a major cause of morbidity and mortality. Haemorrhage occurs less frequently and is particularly associated with platelet counts in excess of 1500 x 10^9/L and acquired von Willebrand disease.

Initial management should address lifestyle issues and risk factors associated with vascular events, including smoking, diabetes, hypertension and hyperlipidaemia. Most patients would benefit from 75mg aspirin daily or alternative anti-platelet drugs. The exceptions are those with active haemorrhage, aspirin intolerance, active or previous peptic ulcer disease, and, in aspirin, should be used with caution in those patients with platelets >1000 x 10^9/L. There is some provisional data that low-risk CALR positive patients may not benefit from aspirin, but at the present time each case should be considered on its own merits.

An acquired von Willebrand disease should be considered in patients with a haemorrhagic phenotype by testing vWF:Ag and ristocetin cofactor activity.

The likelihood of thrombosis and haemorrhage is significantly reduced by therapy to control the platelet count to <400 x 10^9/L. The current gold standard cytoreductive drug is hydroxyurea/hydroxycarbamide (HC). PEG-Interferon (controls the platelet count in the majority of patients and is well tolerated. PegIFN and anagrelide (ANA) have the advantage of being non-leukaemogenic and they preserve fertility. The MRC-PT1 study made a direct comparison between HU and ANA in patients with ET. The results of the high-risk arm suggest that HC + aspirin is a more effective first-line therapy than ANA + aspirin, which was associated with a higher rate of arterial thrombosis, haemorrhage and myelofibrotic transformation. A randomised trial to compare HU versus IFN would be of benefit to further evidence-based practice.

As survival in ET is long and cytoreductive agents have a poor side-effect profile, current practice would be to use these agents only in patients with a high risk of thrombosis. This would include patients aged over 60 or with any of the following risk factors: a prior thrombosis, diabetes, hypertension, vascular disease or a platelet count >1500 x 10^9/L. For patients under 40 with none of these risk factors, aspirin alone is probably sufficient. For patients aged between 40 and 60 and lacking any of the risk factors, the management strategy is far from clear. Best practice would be to randomise such patients into an appropriate clinical trial, if available.

7.1.2 Aims of treatment

The aims of treatment are to reduce the incidence of thrombotic and haemorrhagic complications and potentially reduce long-term risk of transformation to myelofibrosis.

7.1.3 Evidence

- HC reduces the incidence of thrombotic episodes in high-risk patients according to a randomised controlled trial (Cortelazzo, *et al.*, 1995).
- IFN usage is based upon retrospective case series (Elliott and Tefferi, 1997; Reilly, 1996; Radin, 2003, Destero *et al* 2019).
- ANA may be inferior to HC according to the results of the high-risk arm of the MRC-PT1 and the EXEL study (Harrison, 2005, Birgegard, 2018)
- Evidence on which to base a management strategy for patients aged 40-59 with no high-risk features has recently been published (Godfrey, 2018).
- There is evidence that HC reduces long-term risk of transformation to myelofibrosis in PV, although there is no direct evidence for ET (Najean, *et al.*, 1996).
- Patients who are resistant or intolerant to HU have a worse prognosis (Hernandez-Boluda, 2015).

7.1.4 Treatment protocol

- Identify and aggressively manage all reversible risk factors for arterial disease including smoking, hypercholesterolaemia, hypertension and diabetes. Responsibility for this to be defined with primary care.
- Document MPN related symptoms.
- Aspirin for all in absence of contraindications as above. Consider screen for acquired von Willebrand disease in those with platelets >1000 x 10^9/L. Consider clopidogrel if intolerant of aspirin.

Evidence grade level overall Ib-III

High-risk patients

First-line therapy is HC, pegylated IFN should be considered in younger patients.

> *Ensure counselling of all patients of reproductive age regarding teratogenicity. Uncertain effects upon fertility in long-term use and reiterate necessity for contraception (see above).*

Evidence grade level Ib

Second-line therapy (in those patients who are refractory/intolerant to first-line therapy or developing PMF or progressive splenomegaly):

- Patients aged >70 years, consider busulfan or combination therapy with ANA and HC.

- Patients aged <70 years, consider ANA or combination therapy with ANA and HU or consider pegylated interferon alpha 2A.
- Emerging evidence for the use of JAKi – consider clinical trials of novel therapies

Evidence grade level III

Intermediate- and low-risk patients

The MRC-PT1 trial demonstrated no benefit for the addition of HC to aspirin for intermediate risk patients (age 40-60). Low-risk patients may receive aspirin but this may not be indicated on a risk assessment basis for *CALR* mutated patients. **Discuss with consultant.** Consider recruiting into an appropriate clinical trial or research study.

Treatment Summary Box: Essential thrombocythaemia

- **ALL** patients – assess and manage cardiovascular risk factor; screen for disease-related symptoms
- **TREAT WITH** low dose aspirin (unless contraindicated)
- HIGH-RISK PATIENTS*

  >60* years

  1st line: hydroxycarbamide or pegylated IFN in selected cases

  2nd line: consider clinical trial or pegylated interferon**, anagrelide*** alone or in combination; if

  >75 years busulfan or ^{32}P

  <60* years

  1st line: hydroxycarbamide or pegylated interferon**

  2nd line: consider clinical trial; pegylated interferon**, anagrelide*** alone or in combination.

* Treatment recommendations made for high-risk patients only, high-quality clear evidence for low or intermediate risk ET or PV management is unclear.

** Not currently licensed but NHSE funded for this indication.

*** Current British guidelines recommend regular monitoring of patients treated with anagrelide for the development of fibrosis.[9]

Treatment options

Aggressively manage all reversible risk factors for arterial disease.

Patient leaflets are available for all treatment options from the MPN Voice (www.mpnvoice.org.uk) and the Macmillan websites.

Pre-chemotherapy counselling is available from the CNS/key worker. The counselling session should be followed up one week later with a telephone consultation.

Formal written consent should be obtained for all patients before commencing any cytoreductive therapy (red cell-, white cell- or platelet-controlling drugs) including hydroxycarbamide (hydroxyurea), anagrelide, interferon alpha, ruxolitinib, busulfan or radioactive phosphorus.

Aspirin

75mg per day for all patients without a clear contraindication (asthma, history of peptic ulceration, haemorrhage, platelet count in excess of 1000 x 10^9/L). Clopidogrel 75 mg/day may be used if the patient is intolerant of aspirin.

Hydroxyurea/hydroxycarbamide

Refer to local or regional protocol. HC is the only treatment with demonstrated benefit in a randomised controlled trial; benefit for intermediate-risk patients was assessed in the MRC-PT1 study. Limiting side effects include teratogenicity and the development of a refractory state in 10–15% of patients. There is no published evidence that HC monotherapy is leukaemogenic but HC may enhance the leukaemogenic effect of other cytoreductive agents such as busulfan and ^{32}phosphorus (risk of AML 15–30% if used in combination with alternative leukaemogenic agents (Murphy, *et al*., 1997; Sterkers, *et al*., 1998).

> *Prior to conception, a three-month wash-out period is required. Women should be reviewed, stop HC and discuss alternative treatment if necessary with IFN. Similarly, men wishing to father a child should discontinue HC three months prior to planned conception and discuss treatment if necessary with IFN. Young male patients should be offered sperm cryopreservation before starting this treatment.*

Interferon

Use of pegylated interferon in specific clinical circumstances should be considered as standard of care across London hospitals. IFN reduces the risk of complications in high-risk patients and pegylated IFN is much better tolerated. is a suitable second-line agent and also the only treatment currently used in pregnancy (Harrison, 2002). Pegylated-IFN is better tolerated and is the formulation of choice for these patients.

The relative benefit of HC versus IFN first-line is yet to be determined.

For all interferons, it is important to screen regularly for liver and thyroid disease, as well as active surveillance for depression.

Anagrelide

Refer to local or regional protocol. ANA is currently licensed for high-risk patients as a second-line agent for patients refractory or intolerant of first-line therapy. Limitations include cardiac toxicity and teratogenicity. Preliminary data from the MRC-PT1 study suggest ANA is not as effective as HU in preventing thrombotic and haemorrhagic complications, and is associated with greater risk of progression to myelofibrosis. **The risk of bleeding should be assessed and considered prior to the concomitant use of aspirin.**

ANA may be usefully given in combination with HU in some patients.

> *Prior to commencing ANA, all patients must have a chest x-ray and ECG. An echocardiogram should be performed in those with a previous cardiac history or abnormal ECG or increased cardiothoracic ratio on chest x-ray. Further evaluation is required if patients become symptomatic. Consider referral to a cardiologist if indicated.*

Busulfan

Refer to local or regional protocol. Busulfan is a historical treatment associated with a higher incidence of leukaemic transformation than treatment with hydroxycarbamide. Other serious complications are idiopathic pulmonary fibrosis and aplasia. Use is limited in general to second line in patients over 75 years of age due to the associated risk of leukaemia. **Discuss with consultant haematologist.**

^{32}Phosphorus

Phosphorus is a historical treatment which has an even higher incidence of leukaemic transformation than treatment with busulfan. Hence, it is reserved for the very elderly or patients in whom one cannot ensure compliance with medications. A medical consent generated by nuclear medicine should be completed by the haematology department. **Discuss with consultant haematologist.**

JAK inhibitors/HDACs/ Other novel therapies

For refractory or intolerant patients, consider entry into a clinical trial for use of a novel agent in this setting.

7.1.5 Situations where alternative agents to HC may be needed

i. **Inability to suppress platelet count to normal range without causing anaemia or neutropenia – i.e. HC-refractory (see Annex 3, Table B)**

   Consider relaxing platelet target to <600 x 10^9/L or switching to alternative agent (see below). Combining low-dose anagrelide with HC can be effective in this setting.

ii. **Development of HC-related side-effects**

   If mild gastrointestinal symptoms or rash, consider temporarily reducing the HC dose then slowly re-increasing as necessary, with appropriate symptom-management.

   For more serious effects, including leg or severe oral ulceration, actinic keratosis, squamous cell carcinoma, and nail changes, HC should be stopped and an alternative agent started if feasible.

Patient concerns regarding leukaemogenicity of HC

Patients should be counselled that there is no available conclusive evidence that HC is associated with an increased risk of leukaemic transformation *per se*, despite extensive experience of the drug and a large Swedish registry-based study (Bjorkholm, *et al.*, 2011). If patients remain reluctant to take HC, they should be offered an alternative drug.

Patients who are pregnant or lactating, or planning to become pregnant or father children in the near future

HC should be stopped and patients offered pegylated interferon-alpha therapy. See section 9.2 on ‘ET in pregnancy’.

7.2 Polycythaemia vera (PV

7.2.1 Management and prognosis

Thrombosis is the major cause of death in untreated patients whose median survival is only 18 months. Control of the elevated PCV is achieved by repeated venesection or cytoreductive therapy (especially if the platelet count is elevated). The target HCT is <0.45 (venesections should be timed to keep HCT <0.45; this target may be reduced in patients remaining symptomatic), and platelets <400 x 10^9/L. Most patients would benefit from 75mg aspirin daily or alternative anti-platelet drugs. The exceptions are those with active haemorrhage, aspirin intolerance, active or previous peptic ulcer disease, and, in aspirin should be used with caution in those patients with platelets >1000 x 10^9/L.

An acquired von Willebrand disease should be considered in patients with a haemorrhagic phenotype by testing vWF:Ag and ristocetin cofactor activity.

HC is the standard cytoreductive drug used to treat PV and other MPNs. It is generally well tolerated but there is some anxiety that it might increase the risk of leukaemia. Historically ^{32}Phosphorus and busulfan were used, but their use is restricted because of their well-defined leukaemogenic potential. Alternative therapies include pegylated-IFN, ANA for those with marked thrombocytosis and ruxolitinib, with the dual advantages of preserving fertility and being non-leukaemogenic.

7.2.2 Aims of treatment

The aim is to reduce the incidence of thrombotic and haemorrhagic complications and the long-term risk of transformation to myelofibrosis.

7.2.3 Evidence

- Control of haematocrit and thrombocytosis reduces thrombotic complications according to the PVSG trials (Berk, 1986; Najean, 1994).
- Retrospective case series support the use of IFN and ANA (Reilly, 1996; Radin, 2003; Anagrelide Study Group, 1992; Kiladjian, 2008).
- Cytoreductive therapy compared to venesection alone reduces the incidence of myelofibrosis (Najean, 1996).
- Patients with a high platelet count, high white cell count are at particular risk of MF (Najean, 1996).
- Patients with abnormal cytogenetics and high white cell count are at risk of developing AML (Tefferi, 2013).
- Patients who are resistant or intolerant to HU tend to have a worse prognosis (Alvarez-Larran, 2015).
- Target HCT is 0.45 (Barbui, *et al.*, 2013).
- White cell count >11 has an impact upon thrombotic risk (Barbui, 2016).
- Ruxolitinib is of benefit for patients who are resistant/intolerant to HU (Vannucchi, 2015).

7.2.4 Treatment protocol

- Aggressively manage all reversible risk factors for cardiovascular disease.
- Aspirin should be considered in all cases in absence of contra-indications as above.

Evidence grade level Ib

High-risk patients

First-line therapy is HC or pegylated interferon.

> *Ensure counselling of all patients of reproductive age regarding teratogenicity potential and long-term effects upon fertility and reiterate necessity for contraception.*

Evidence grade level III

Second-line therapy (in those patients refractory/intolerant to first-line therapy or developing PMF or progressive splenomegaly on hydroxycarbamide):

- Patients aged >75 years – busulfan or consider combination therapy with HU and ANA or PEG-interferon, but see restrictions above.
- Patients aged <75 years – consider PEG-IFN or consider combination therapy with HU and ANA.
- Consider novel agents such as JAKi in clinical trials/ access scheme
- Or treatment as for myelofibrosis if developing.

Evidence grade level IV

Low-risk patients

First-line treatment is venesection alone. Monitor regularly and if repeat BM suggests development of myelofibrosis, or if spleen enlarges add cytoreductive therapy as for high-risk patients above is reasonable. Ruxolitinib should be given to those with PPV-MF if there is an indication to do so (see MF section).

Evidence grade level IV

Treatment Summary Box: Polycythaemia vera

- **ALL** patients
  - Assess for and manage cardiovascular risk factors
  - Screen for disease-related symptoms
  - **Treat** with low dose aspirin (unless contraindicated)
- **Low-risk patients**
  - Venesect to target PCV <0.45
- Consider cytoreduction if low risk + progressive thrombocytosis (plts>1000) leucocytosis (WBC>15), poor control of Hct, poor tolerance to v/section, systemic symptoms, haemorrhagic symptoms,
- **High-risk patients**
  - >65* years:
    - 1st line: clinical trial or HC or peg interferon
    - 2nd line: clinical trial or pegylated interferon**,
    - if >75 years busulfan or ^{32}P
  - <65* years:
    - 1st line: clinical trial or pegylated interferon or HC**
    - 2nd line: consider clinical trial or pegylated interferon, HC
-

* Treatment recommendations made for high-risk patients only, high-quality clear evidence for low- or intermediate-risk ET or PV management is unclear.

** Not currently licensed for this indication.

*** Current British guidelines recommend regular monitoring of patients treated with anagrelide for the development of fibrosis.[9]

Treatment options

Patient leaflets are available for all treatment options from www.mpnvoice.org.uk or the Macmillan website.

Pre-chemotherapy counselling is available from the CNS/key worker. The counselling session should be followed up one week later with a telephone consultation.

Formal written consent should be obtained for all patients before commencing any cytoreductive therapy (red cell-, white cell- or platelet-controlling drugs) including hydroxyurea (hydroxycarbamide), anagrelide, pegylated- interferon, ruxolitinib, busulfan or radioactive phosphorus.

Venesection

To maintain PCV less than 0.45.

Aspirin

A dose of 75mg per day should be considered for all patients without clear contraindication (asthma, history of peptic ulceration, haemorrhage, platelet count in excess of 1000 x 10^9/L). Clopidogrel is a suitable alternative.

Hydroxyurea/hydroxycarbamide (HU)

Refer to local chemotherapy protocol. The benefit of HC is demonstrated in the PVSG study (Berk, 1986, *GISP*). Limiting side effects include teratogenicity and the development of a refractory state in 10–15% of patients. There is no published evidence that HC monotherapy is leukaemogenic but HC may enhance the leukaemogenic effect of other cytoreductive agents such as busulfan and ^{32}phosphorus (risk of AML 15–30% if used in in combination with alternative leukaemogenic agents) (Murphy, *et al*., 1997; Sterkers, *et al*., 1998).

> *Prior to conception, a three-month wash-out period is required. Women should be reviewed, stop HU and discuss alternative treatment if appropriate with IFN. Similarly, men wishing to father a child should discontinue HU three months prior to planned conception and discuss treatment if appropriate with IFN. Sperm banking should be considered for young males starting HU.*

Pegylated-interferon

Use of pegylated-interferon in specific clinical circumstances should be considered as standard of care across London hospitals. This agent has a similar utility to conventional interferon but has much less in the way of side effects. It is currently approved for treatment of patients who are refractory or intolerant to first-line therapy, and there are some early data suggesting it is useful in this setting (Rea, *et al.*, 2009). Intolerance to therapy would include development of side effects that would lead to therapy introduction, and refractory disease is defined as inability to reach therapeutic targets without causing dose-limiting toxicity or unacceptable cytopenia. There are also provisional data suggesting it may induce molecular remissions in some patients with ET or PV (Kiladjian, *et al*., 2008; Masarova, *et al.*, 2017) and also significant responses in patients with PMF (Ianotto, *et al.*, 2009; Silver, *et al*., 2017).

For all interferons, it is important to screen regularly for liver and thyroid disease, as well as active surveillance for depression.

Anagrelide

Refer to the local chemotherapy protocol. There is evidence of a reduction of complications in high-risk ET patients in observational but not in comparative studies. The numbers of patients with PV in these studies is small (Anagrelide Study Group, 1992). See further comments under section 7.1: Essential thrombocythaemia. **The risk of bleeding should be assessed and considered prior to the concomitant use of aspirin.**

ANA may be used in combination with HU in selected patients.

All patients must have a chest x-ray and ECG before commencing ANA.
An echocardiogram should be performed in those with a previous cardiac history or abnormal ECG or increased cardiothoracic ratio on chest x-ray. Consider follow-up evaluation if patients become symptomatic. Consider referral to a cardiologist if indicated.

Busulfan

Refer to the local chemotherapy protocol. Busulfan is a historical treatment associated with a higher incidence of leukaemic transformation than treatment with hydroxycarbamide is. Other serious complications are idiopathic pulmonary fibrosis and aplasia. Its use is limited to patients over 65 due to the associated risk of leukaemia, in whom it is a second-line therapy in those patients refractory/intolerant to HU. **Discuss with consultant haematologist.**

^{32}Phosphorus

Phosphorus is a historical treatment which has an even higher incidence of leukaemic transformation than treatment with busulfan. Hence it is reserved for the very elderly or patients in whom one cannot ensure compliance with medications. Orders are via EPR; a medical consent generated by nuclear medicine should be completed by the haematology department. **Discuss with consultant haematologist.**

Ruxolitinib, a JAK1 and JAK2 inhibitor which is approved for MF, has also been approved but is not currently reimbursed for HU resistant/intolerant PV patients whose symptoms are severe and uncontrolled with standard therapy (NB not funded in UK). These patients should be discussed in an MDM and if the drug seems appropriate, an IFR or compassionate use application would be needed.

7.3 Primary (or secondary) myelofibrosis (PMF, PPV-MF, PET-MF

7.3.1 Management and prognosis

Aims of treatment encompass a reduction in disease-associated symptoms and splenomegaly, reducing the incidence of thrombotic or haemorrhagic events and ideally reducing disease progression and increasing overall survival. Therapeutic strategies mainly involve symptom-related management and the last decade has seen an increase in the currently available agents for the management of myelofibrosis. Many patients may be suitable for JAK inhibitor treatment, with androgens or erythropoietin therapy for some where appropriate. Supportive therapy with red cell transfusions and treatment of infection is a mainstay where required. Hydroxycarbamide may be useful in some proliferative cases and can help to aid reductions in splenomegaly. In advanced disease, splenectomy is an option but has significant morbidity and indeed mortality rates and is not generally recommended; splenic irradiation may be useful in some. Allogeneic stem cell transplantation may cure a small number of patients but, due to high procedure-related mortality, careful patient selection is critical in transplant-eligible cases who have a good donor and centres should adhere to the current EBMT/ELN guidelines.

7.3.2 Aims of treatment

- Control symptoms of disease
- Reduce incidence of thrombotic and haemorrhagic complications
- Address anaemia where present and reduce requirement for transfusions
- Reduce disease progression.
- Improvement in Overalll Survival

7.3.3 Treatment protocol

Intermediate- and high-risk patients

Consider therapeutic agents below as per specific indications and clinical phenotype. Consider suitability for clinical trials. Tissue type and refer for stem cell transplant discussion if less than 65–70 years dependent on local practice and sufficiently fit – deemed to be 'transplant-eligible'.

Low-risk patients

Tissue type siblings if under 60-65 to potentially inform future therapy.

If progress, treat as for intermediate/ high-risk patient.

Evidence grade level IV

7.3.4 Treatment options

Also see comments under section 7.1: Essential thrombocythaemia.

Aggressively manage all reversible risk factors for arterial disease.

Patient leaflets are available for all treatment options from the Macmillan website and MPN voice and Blood wise.

Pre-chemotherapy counselling is available from the CNS/key worker.

Counselling session should be followed up one week later.

> *Formal written consent should be obtained for all patients before commencing any cytoreductive therapy (red cell-, white cell- or platelet-controlling drugs) including hydroxyurea (hydroxycarbamide), ruxolitinib, anagrelide, pegylated interferon, busulfan or radioactive phosphorus.*

Aspirin

75mg per day should be considered in all patients without clear contraindication (asthma, history of peptic ulceration, haemorrhage, laboratory evidence of acquired von Willebrand disease, or a platelet count in excess of 1000 or a platelet count <50 x 10^9/L).

Ruxolitinib

The JAK2 inhibitor ruxolitinib is currently available for first- or second-line use in symptomatic MF patients/ patients with problematic splenomegaly for IPSS or DIPPS Intermediate 2 and above individuals. Evidence from the COMFORT and COMFORT-2 studies indicates that ruxolitinib is

effective in reducing spleen size and associated symptoms and improves overall quality of life as well as overall survival (Harrison, 2016; Verstovsek, 2017). Refer to the local chemotherapy protocol. In brief,

- A highly effective drug for many patients and much more clinical familiarity
- Anaemia and thrombocytopenia may limit effective dosing
- Infections: 5% herpes zoster, atypical infections e.g. reactivation of TB but low incidence
- Recent link to slightly higher risk of NHL reported – requires more clarity
- Lack of evidence of disease modification in low-risk MF at present
- Definition of Ruxolitinib failure variable in clinical trials, unclear in clinical practice

NB screening for hepatitis and HIV is required prior to starting this agent. Patients with anaemia or thrombocytopenia require careful monitoring, Ruxolitinib can be used with caution in patients with platelets <50 x 10^9/L in the absence of bleeding. Here combination with danazol may be useful. For anaemic patients combination with Danazol or ESA may be beneficial.

Hydroxyurea/hydroxycarbamide (HC)

Refer to the local chemotherapy protocol. Limiting side effects include teratogenicity and the development of a refractory state in 10–15% of patients. There is no published evidence that HU monotherapy is leukaemogenic but HU may enhance the leukaemogenic effect of other cytoreductive agents such as busulfan and ^{32}phosphorus (risk of AML 15–30% if used in combination with alternative leukaemogenic agents (Murphy, *et al.*, 1997; Sterkers, *et al.*, 1998).

> *Prior to conception, a three-month wash-out period is required. Women should be reviewed, stop HU and discuss alternative treatment if appropriate with IFN. Similarly, men wishing to father a child should discontinue HU three months prior to planned conception and discuss treatment if appropriate with IFN. Sperm banking should be considered for young males.*

Thalidomide

Previous evidence suggests that low doses of thalidomide (50mg) in combination with a reducing dose of prednisolone commencing 1mg/kg may be beneficial and less toxic than doses used previously (Mesa, 2003; Giovanni, 2002). Some patients develop worsening thrombocytosis and extramedullary haemopoiesis. In patients with a previous history of thrombosis, low molecular weight heparin prophylaxis should be considered. All thalidomide is prescribed via the Pharmion risk management system by a registered prescriber. **This is an unlicensed indication for thalidomide and is not funded by NHS England**. The use of this agent is low given the low rates of efficacy and potential complications.

Pegylated-interferon

This agent has a similar utility to conventional interferon. It is currently approved for treatment of patients who are refractory or intolerant to first-line therapy. There are some early data suggesting it is useful in this setting (Rea, *et al.*, 2009). Intolerance to therapy would include development of side effects that would lead to therapy introduction, and refractory disease is defined as inability to reach therapeutic targets without causing dose-limiting toxicity or unacceptable cytopenia. There

are also provisional data suggesting it may induce molecular remissions in some patients with ET or PV (Kiladjian, *et al.*, 2008; Masarova, *et al*., 2017) and also significant responses in patients with PMF (Ianotto, *et al.*, 2009; Silver, *et al*., 2017). Refer to the local chemotherapy protocol.

For all interferons, it is important to screen for liver and thyroid disease, as well as surveillance for depression.

Busulfan

Refer to the local chemotherapy protocol. Busulfan is a historical treatment associated with a higher incidence of leukaemic transformation than treatment with hydroxycarbamide. Other serious complications are idiopathic pulmonary fibrosis and aplasia. Its use is limited to patients over 70 due to the associated risk of leukaemia. It may be a higher-line therapy in those patients refractory/intolerant to HU with progressive cytosis. **Discuss with consultant haematologist**.

Erythropoietin

Erythroid Stimulating Agents can have a role in improving anaemia in MF. Baseline EPO levels should be checked prior to commencement of ruxolitinib to assess if these are predictive of response. **See section 8.1below. Discuss with consultant haematologist and pharmacy.**

Haematopoietic stem cell transplantation (HSCT)

There is evidence that well selected transplant eligible patients may benefit from HSCT and this remains the only curative procedure. Refer patients at diagnosis, if they are a suitable candidate, in line with BSBMT and EBMT/ELN recommendations. As suggested by the current European LeukaemiaNet/ EBMT consensus statement generated by an international panel of experts several years ago ‘Patients with intermediate-2- or high-risk disease and age <70 years should be considered as candidates for allo-SCT. Patients with intermediate-1-risk disease and age <65 years should be considered as candidates if they present with either refractory, transfusion-dependent anemia, or a percentage of blasts in peripheral blood (PB) >2%, or adverse cytogenetics’ (Kroger *et al,* 2015). Of note, by nature of the disease, many of the patients referred for consideration of alloSCT are of more advanced age, some with significant co-morbidities. Both poor performance status and high HCT-specific comorbidity index scores have been shown to have a significant adverse impact on survival. Hence, detailed review by a Transplant Physician is warranted.

Investigational agents

Other JAK2 inhibitors are in clinical trials, as are combinations of JAK2 inhibitors and pan-deacetylase inhibitors in addition to a wide array of other novel agents. JAK2 inhibitors have thus far demonstrated significant and sustained improvement in splenomegaly, disease-related symptoms, functioning and quality of life. They have been well tolerated with acceptable and well recognised toxicities.

7.4 MPN in accelerated or blast phase

Accelerated phase (AP) MPN is represented by circulating blasts 10-19% or similar quantities in the bone marrow. Patients with these features are a very high risk of developing blast phase disease (persistently >20% blasts in blood or bone marrow). AP is usually a precursor to BP-median survival of AP is <2 years and MP 3-5 months. Allogeneic stem cell transplant is the

definitive treatment for these. Upon diagnosis of AP/BP a donor search should be initiated for suitable patients. For patients suitable for HSCT azacytidine or intensive chemotherapy may be used as bridge to transplant. Otherwise the role of intensive chemotherapy is limited.

For patients unsuitable or unwilling for intensive treatment the following treatments options should be considered:

Low-dose cytarabine

The dosing is as per local hospital recommendations**.**

Azacitidine

Azacitidine has been used in some patients with accelerated or transformed MF with success – 75mg/m^2 for seven days (or 5-2-2 regimen) is a suitable starting dose. This should be discussed with a consultant haematologist. With 4-6 cycles of azacytidine, overall response was 52%, 24% achieved CR. Time to response may be long and response duration is variable, median 9 months after which a proportion may revert to chronic stage. Treatment should be continued to relapse/progression. Treatment should ideally not be modified for cytopaenia and 4 weekly schedule should be maintained.

The role of ruxolitinib as single agent is not encouraging; combination of Azacytidine and ruxolitinib has been tried with success (in a clinical trial or a patient receiving Ruxolitinib who transforms).

Myeloid gene NGS analysis can help plan treatment as inhibitor therapy such as IDH1 or 2 mutation can be used. Patients should be discussed with specialist centres for access to these drugs.

This is an area of unmet need where clinical trials are needed.

(Odenike, 2018)

7.5 Fertility

> *Management protocols for women in pregnancy and in the three months before conception are more complex and individualised. These cases should be discussed with a consultant haematologist experienced in such cases.* FERTILITY INDUCTION MUST BE DISCUSSED WITH CONSULTANT AND TREATED AT SPECIALISED CENTRES

For young patients with MPN due to undergo AML induction-type chemotherapy and/or an HSCT, the options for fertility preservation should be discussed and the patient referred to a fertility specialist for preservation of sperm and ovarian tissue or fertilised embryos. This should also be considered for young patients starting HU. Expert onco-fertility advice should be considered in line with guidance and recommendations for referral to fertility services.

8 Supportive Care

8.1 Anaemia

Red cell transfusions may be required in addition to dose-modification of cytoreductive medication(s) (see also Table 7). Threshold Hb needs to be individualised but in general a threshold of 80g/L is appropriate. Routine iron chelation is not recommended. If EPO levels less than 200u/L, rEPO or biosimilar may be commenced at 10,000 u three times a week (or darbepoietin 150ug/wk), double dose after 1-2 months in absence of response. Discontinue EPO if no response in 3-4 months.

If EPO levels elevated, danazol 200 mg/day escalating to 600-800 mg/day (800 mg/day for >80kg wt) over 6-8 weeks. Minimum 6 months treatment. Responding patients should receive a further 6 months of 400mg/day and then taper dose to minimum required to maintain response. Monthly LFT, ultrasound liver 6-12 monthly. Men must be screened for prostate cancer before and during therapy.

Alternatively, thalidomide 50-100mg, sometimes with prednisolone, may be helpful.

8.2 Haemostasis and thrombosis

VTE: For thrombotic events, anticoagulate as per local protocols and ensure counts are well controlled to prevent future events. For secondary prophylaxis of VTE, use long-term anticoagulation. The role of primary prophylaxis in patients at high risk of VTE has to be considered on an individual basis. The use of DOACs, and combined use of VKA and aspirin, have not been studied in detail as yet.

Arterial thrombosis: For primary prophylaxis, see each specific disease entity. For secondary prophylaxis, use local cardiac or cerebrovascular protocols. Consider switching from aspirin to clopidogrel if arterial events are not prevented by aspirin. Good quality data on aspirin resistance are lacking and the use of dual anti-platelet therapy in MPN has not been studied.

Patients on clopidogrel require cessation of the drug for 5 days pre-procedures with moderate to high risk of bleeding. Patients on aspirin may continue the drug through minor procedures depending on bleeding versus thrombotic risk. Bridging of VKA is required if VTE is <3 months old.

8.3 Hyperviscosity syndrome

Urgent platelet apheresis or red cell apheresis can be undertaken if high counts are causing symptoms of hyperviscosity. Cytoreductive therapy must be initiated or optimised simultaneously.

8.4 Infection

Local protocols should be followed for treatment of infections and prophylaxis.

8.5 Pain management

For symptomatic splenomegaly, see section 7: Treatment for disease-specific treatment options (hydroxycarbamide versus surgery versus splenic irradiation versus ruxolitinib or other chemotherapy in MF).

People reporting pain should be considered for non-pharmacological intervention including, but not limited to, TENS (transcutaneous electrical nerve stimulation), complementary therapy and psychological intervention such as mindfulness.

8.6 Other symptom control

Table 7: Symptomatic therapy for MF

Clinical need	Drugs/Intervention	
Anaemia	Corticosteroids Danazol ESA if EPO level <200IU Transfusion	Thalidomide + steroids (unlicensed indication) Clinical Trials
Symptomatic splenomegaly	Ruxolitinib Hydroxycarbamide Novel Therapies in Clinical Trials e.g other JAKi	Splenectomy Splenic radiation
Extramedullary haematopoiesis	Radiation therapy and ? ruxolitinib role	
Risk of thrombosis or recurrence	Low-dose ASA	Hydroxyurea
Constitutional symptoms/QoL	Ruxolitinib and consider bisphosphonates for bone pain	
Pruritus	Antihistamines, fluoxetine, PUVA, Ruxolitinib liaise with dermatologist	
Risk of leukaemia transformation	None specifically directed	
Improved survival	Ruxolitinib Allogeneic HSCT	

8.7 Breathlessness

- Any inpatient showing signs of respiratory distress should be assessed by a physician with knowledge of treatment for patients with MPN and, if appropriate, referred for respiratory physiotherapy assessment in accordance with local on-call guidelines, unless of overt metabolic cause. Consider VTE and pulmonary hypertension.
- Ongoing breathlessness management strategies can be provided by occupational therapy or physiotherapy.

8.8 Weight loss

- A screening tool for the assessment of dietary issues should be completed weekly for inpatients and, if issues are identified, a referral should be made to a specialist dietitian.
- Referral for specialist dietetic input should be made in the following instances:
  - Any patient with neutropenia should be provided with information and education on the neutropenic diet and be referred to a specialist dietitian.
  - If artificial feeding is being considered, a referral to the specialist dietitian should be made.
  - Any patient with mucositis should be referred for dietetic assessment, as well as for specialist speech and language assessment.

- Weight loss/malnutrition should be identified through weekly screening of inpatients.

8.9 Cardiovascular risk assessment

All patients require a formal CV risk assessment at baseline and yearly. The following CV risk factors must be assessed: smoking, diabetes, hypertension, hyperlipidemia. Primary prophylaxis such as statins should be provided based on national recommendations.

Patients should have CV risk factors optimally controlled by primary care or CV specialists in secondary care.

Primary care should be specifically informed of CV risk posed by MPN to the patient.

8.10 Complex symptom management

- Discuss with specialist palliative care team for advice on symptom management, e.g. pain, mucositis when there is no/poor response to standard interventions. Patients with accelerated or transformed MF may benefit from palliative care support. Where appropriate, referral can be made to the specialist palliative care team.
- Irradiation therapy can be used for symptom control for bone pain, splenomegaly and rare for pulmonary hypertension.

9 Special circumstances

9.1 Splanchnic vein thrombosis

- Patients with splanchnic vein thrombosis should have a blood count and mutation analysis for MPN related mutations. If idiopathic, a bone marrow assessment should be considered and undertaken only when heparin or warfarin may be safely withheld. Bridging anticoagulation should be used if the thrombosis is recent (eg < 1 year)
- MPN may be masked in SVT patients due to haemodilution and splenomegaly associated with SVT.
- MPN with high blood counts should be treated with venesection and chemotherapy to control the blood counts in therapeutic range. Iron deficiency is frequent due to GI blood loss and tolerance to chemotherapy is affected by splenomegaly and baseline cytopaenia.
- There is lack of evidence on the role of marrow modifying drugs in patients with JAK2 V617F mutation without MPN phenotype.
- All patients should be anticoagulated with heparin in the acute setting, followed by warfarin. Patients should be considered for long-term anticoagulation based on risk-benefit analysis.
- In patients with incidental detection of SVT anticoagulation in the long-term should be considered based on risk-benefit analysis.
- Patients should have access to tertiary level hepatologist and haematologist for shared care in the acute and chronic setting. Patients with acute thrombosis should be discussed and if appropriate, transferred promptly to tertiary hepatobiliary service. See schema and protocol in Annex 3, Flowchart 1.

9.2 Pregnancy

- Refer to specialist obstetrician, serial US monitoring, control counts with IFN if past h/o miscarriage or MPN-related maternal morbidity or high risk of thrombosis. Decide if the

pregnancy is high- or low-risk and discuss with an experienced clinician. Antenatal aspirin +/-, post-natal LMWH 6 weeks for low-risk pregnancy. See Annex 6 for further details regarding high-risk pregnancies.

- If bleeding phenotype, provide tranexamic acid post third stage.

9.3 Peri-operative management

Patients with MPN are at increased risk of both post operative bleeding and thrombosis. Management of these patients should be individualised considering thrombotic/bleeding risk based on disease, patient and procedure factors. Controlling platelet counts pre-operatively to a target of <400 x 109/l should be considered in ET patients undergoing significant surgery (e.g. GA time >90 minutes) or with significant bleeding risk. Local guidelines for peri-operative management of anticoagulation, anti-platelet agents and VTE prevention should be followed. Surgical blood loss and post-operative infection may result in worsening thrombocytosis and should be managed according to the root cause.

9.4 Acute stroke presentation

Acute stroke may be the presenting feature of the MPNs. The mainstay of treatment is as for patients with stroke in the non-MPN setting. Consideration should be given to haemodilution and venesection (PRV) or plateletpheresis (ET) (see section 8.2, 8.3)

For patients with known MPNs cytoreduction should be started in parallel with conventional treatment.

9.5 Treatment summary and care plan

Patients with MPN are followed for life or have supervised care by a haematologist experienced in such disorders. The MDT outcome form and clinic letters will serve to communicate new lines of treatment/change of treatment with the GP.

Treatment summaries should therefore be agreed when there are any significant changes in treatment and follow-up plans. HNAs should be offered through follow-up, with a care plan completed to document the plans to address the issues raised by the patient.

There are two related but distinct documents which patients should be given when there are changes in treatment:

- A **treatment summary** provides a summary of the cancer treatments received by the end of the first treatment, planned follow-ups (including mechanisms for these), and signs and symptoms of which to be aware. Their aim is to provide information not only to the patient, but also to the GP about possible consequences of cancer and its treatment, signs of recurrence and other important information.
- A **care plan** is generated as a result of an HNA and is the agreed plan between the patient and healthcare professional about how the identified areas of concern will be addressed. This may cover provision of information (e.g. through an information prescription), onward referral for specialist assessment and intervention (e.g. breathlessness management), or things which the patient themselves can do (e.g. contact their HR department about graduated return to work options).

10 Follow-up Arrangements

Monitoring of blood counts and renal and liver function should occur according to treatment regimen and patient risk factors by practitioners experienced with these drugs. Telephone and/or nurse-led clinics or prescribing with agreement of the GP (using formalised protocols) may also be used for those patients who are stable and reliable. Shared care arrangements can be made between the haematology unit and the local GP for appropriate patients and local guidelines should be followed for such.

11 End-of-life Care

For older patients and in those with high-risk disease, discussions regarding prognosis and treatment options should also include discussions on end-of-life care. These are to facilitate transitions between active disease-modifying therapy and clinical trials, to supportive care only at the time of disease progression/non-response. Care may be required from specialist palliative care teams.

The named CNS/key worker, patient, family members and palliative care teams, as well as members of the inpatient ward team, may be involved. Clear documentation of the discussion with guidance to the treating teams is helpful in communicating these discussions and outputs to the wider team that may care for the individual.

12 Data Requirements

Accurate data collection is essential to monitor outcomes, and the collection of this information, particularly clinical data, remains the responsibility of the members of the multidisciplinary team with support from a data manager. Haematology services are required to submit data to nationally mandated datasets for all patients diagnosed with haematological cancer; further details on these datasets are available in Annex 2).

All patients should be listed on a local database with a basic dataset.

Dataset:

Name/demographics

Diagnosis

Mutation

VTE yes/no location year

Arterial thr yes/no location year

Treatment 1st line/2nd line/3rd line

Annual SAF score; CR/PR/NR

Alive/dead

References

1. Barbui T, Barosi G, Birgegard G, Cervantes F, Finazzi G, Griesshammer M, *et al*. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2011;**29**(6):761–70.
2. Nangalia J, Massie CE, Baxter EJ, Nice FL, Gundem G, Wedge DC, *et al*. Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2. *N Engl J Med.* 2013;**369**(25):2391–405.
3. Klampfl T, Gisslinger H, Harutyunyan AS, Nivarthi H, Rumi E, Milosevic JD, *et al*. Somatic mutations of calreticulin in myeloproliferative neoplasms. *N Engl J Med.* 2013;**369**(25):2379–90.
4. Barbui T, Thiele J, Vannucchi AM, Tefferi A. Problems and pitfalls regarding WHO-defined diagnosis of early/prefibrotic primary myelofibrosis versus essential thrombocythemia. *Leukemia*. 2013;**27**(10):1953–8.
5. Landolfi R, Marchioli R, Kutti J, Gisslinger H, Tognoni G, Patrono C, *et al*. Efficacy and safety of low-dose aspirin in polycythemia vera. *N Engl J Med.* 2004;**350**(2):114–24.
6. Harrison C, Barbui T. Aspirin in low-risk essential thrombocythemia, not so simple after all? *Leuk Res.* 2011;**35**(3):286–9.
7. Marchioli R, Finazzi G, Specchia G, Cacciola R, Cavazzina R, Cilloni D, *et al.* Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med.* 2013;**368**(1):22–33.
8. McMullin MF, Harrison CN, Kiladjian JJ. Treatment target in polycythemia vera. *N Engl J Med*. 2013;**368**(16):1554–5.
9. Harrison CN, Bareford D, Butt N, Campbell P, Conneally E, Drummond M, *et al*. Guideline for investigation and management of adults and children presenting with a thrombocytosis. *Br J Haematol.* 2010;**149**(3):352–75.
10. Passamonti F. How I treat polycythemia vera. *Blood*. 2012;120(2):275–84.
11. Barbui T, Finazzi G, Carobbio A, Thiele J, Passamonti F, Rumi E, *et al*. Development and validation of an International Prognostic Score of thrombosis in World Health Organization-essential thrombocythemia (IPSET-thrombosis). *Blood*. 2012;120(26):5128–33; quiz 252.
12. Tefferi A, Rumi E, Finazzi G, Gisslinger H, Vannucchi AM, Rodeghiero F, *et al.* Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. *Leukemia*. 2013;**27**(9):1874–81.
13. Campbell PJ, MacLean C, Beer PA, Buck G, Wheatley K, Kiladjian JJ, *et al.* Correlation of blood counts with vascular complications in essential thrombocythemia: analysis of the prospective PT1 cohort. *Blood*. 2012 Aug 16;**120**(7):1409–11.
14. Wilkins BS, Erber WN, Bareford D, Buck G, Wheatley K, East CL, *et al.* Bone marrow pathology in essential thrombocythemia: interobserver reliability and utility for identifying disease subtypes. *Blood*. 2008;**111**(1):60–70.
15. Quintas-Cardama A, Kantarjian H, Manshouri T, Luthra R, Estrov Z, Pierce S, *et al.* Pegylated interferon alfa-2a yields high rates of hematologic and molecular response in patients with advanced essential thrombocythemia and polycythemia vera. *J Clin Oncol.* 2009;**27**(32):5418–24.

16. Kiladjian JJ, Cassinat B, Chevret S, Turlure P, Cambier N, Roussel M, *et al.* Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. *Blood*. 2008;**112**(8):3065–72.
17. Barosi G, Mesa R, Finazzi G, Harrison C, Kiladjian JJ, Lengfelder E, *et al.* Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. *Blood*. 2013;**121**(23):4778–81.
18. Barosi G, Birgegard G, Finazzi G, Griesshammer M, Harrison C, Hasselbalch H, *et al.* A unified definition of clinical resistance and intolerance to hydroxycarbamide in polycythaemia vera and primary myelofibrosis: results of a European LeukemiaNet (ELN) consensus process. *Br J Haematol.* 2010;**148**(6):961–3.
19. Barosi G, Besses C, Birgegard G, Briere J, Cervantes F, Finazzi G, *et al.* A unified definition of clinical resistance/intolerance to hydroxyurea in essential thrombocythemia: results of a consensus process by an international working group. *Leukemia*. 2007;**21**(2):277–80.
20. Verstovsek S, Passamonti F, Rambaldi A, Barosi G, Rosen PJ, Levy R, *et al.* Durable responses with the JAK1/JAK2 inhibitor, INCB018424, in patients with polycythemia vera (PV) and essential thrombocythemia (ET) refractory or intolerant to hydroxyurea (HU). *ASH Annual Meeting Abstracts.* 2010;**116**(21):313.
21. Verstovsek S, Passamonti F, Rambaldi A, Barosi G, Rosen PJ, Rumi E, *et al.* A phase 2 study of ruxolitinib, an oral JAK1 and JAK2 inhibitor, in patients with advanced polycythemia vera who are refractory or intolerant to hydroxyurea. *Cancer*. 2013;**120**(4):513–20.
22. Barbui T, Barosi G, Birgegard G, Cervantes F, Finazzi G, Griesshammer M, *et al.* Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol*. 2011;**29**(6):761–70.
23. Reilly JT, McMullin MF, Beer PA, Butt N, Conneally E, Duncombe A, *et al.* Guideline for the diagnosis and management of myelofibrosis. *Br J Haematol.* 2012;**158**(4):453–71.
24. Passamonti F, Cervantes F, Vannucchi AM, Morra E, Rumi E, Pereira A, *et al.* A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood*. 2010;**115**(9):1703–8.
25. Gangat N, Caramazza D, Vaidya R, George G, Begna K, Schwager S, *et al.* DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. *J Clin Oncol.* 2011;**29**(4):392–7.
26. Cervantes F, Dupriez B, Pereira A, Passamonti F, Reilly JT, Morra E, *et al.* New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. *Blood*. 2009;**113**(13):2895–901.
27. McMullin MF, Harrison CN, Ali S, Cargo C, Chen F, Ewing J,*et al*; BSH Committee. A guideline for the diagnosis and management of polycythaemia vera. A British Society for Haematology Guideline. *Br J Haematol.* 2019 ;**184**(2):176-191. Apr;185(1):198.
28. Desterro J, McLornan DP, Curto Garcia N, O'Sullivan J, Alimam S, Keohane C,*et al*. Essential thrombocythaemia treated with recombinant interferon: 'real world' United Kingdom referral centre experience. *Br J Haematol;* 2019; **186(**4):561-564.

29. Birgegård G, Besses C, Griesshammer M, Gugliotta L, Harrison CN, Hamdani M, et al. Treatment of essential thrombocythemia in Europe: a prospective long-term observational study of 3649 high-risk patients in the Evaluation of Anagrelide Efficacy and Long-term Safety study. *Haematologica.* 2018; **103**(1):51-60.
30. Passamonti F, Giorgino T, Mora B, Guglielmelli P, Rumi E, Maffioli M,et al. A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. *Leukemia. 2017* **201**; 31(12):2726-2731.
31. Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, *et al.* A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med.* 2012;**366**(9):799–807.
32. Harrison C, Kiladjian JJ, Al-Ali HK, Gisslinger H, Waltzman R, Stalbovskaya V, *et al.* JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med.* 2012;**366**(9):787–98.
33. Cervantes F, Vannucchi AM, Kiladjian JJ, Al-Ali HK, Sirulnik A, Stalbovskaya V, *et al.* Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. *Blood*. 2013;**122**(25):4047–53.
34. Tefferi A, Pardanani A. Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis. *Mayo Clin Proc.* 2011;**86**(12):1188–91.
35. Verstovsek S, Gotlib J, Levy RS, Gupta V, Dipersio JF, Catalano JV, *et al.* Long-term outcomes of ruxolitinib therapy in patients with myelofibrosis: 3-year update from COMFORT-I. *Blood*. 2013;**122**(21):396.
36. Heine A, Brossart P, Wolf D. Ruxolitinib is a potent immunosuppressive compound: is it time for anti-infective prophylaxis? *Blood*. 2013;**122**(23):3843–4.
37. Passamonti F, Barbui T, Barosi G, Begna K, Cazzola M, Cervantes F, *et al.* Phase 3 study of pomalidomide in myeloproliferative neoplasm (MPN)-associated myelofibrosis with RBC-transfusion-dependence. *Blood*. 2013;**122**(21):394.
38. Ianotto JC, Boyer-Perrard F, Gyan E, Laribi K, Cony-Makhoul P, Demory JL, *et al.* Efficacy and safety of pegylated-interferon alpha-2a in myelofibrosis: a study by the FIM and GEM French cooperative groups. *Br J Haematol*. 2013;**162**(6):783–91.
39. Björkholm M, Derolf ÅR, Hultcrantz M, Kristinsson SY, Ekstrand C, *et al.* Treatment-related risk factors for transformation to acute myeloid leukemia and myelodysplastic syndromes in myeloproliferative neoplasms. *J Clin Oncol.* 2011;**29**(17):2410–2415.
40. Thiele J, Kvasnicka HM, Müllauer L, Buxhofer-Ausch V, Gisslinger B, Gisslinger H. Essential thrombocythemia versus early primary myelofibrosis: a multicenter study to validate the WHO classification. *Blood*. 2011;**117**(21):5710-8.
41. Odenike O. How I treat blast phase of Ph negative myeloproliferative neoplasms. *Blood.* 2018, 132, 22, 2339.

Annex 1: Nurse-led MPN Clinic SOP and Referral Guideline [an example]

[Polycythaemia vera (PV) and essential thrombocythaemia (ET)]

Background

The nurse-led MPN clinic is often established in response to a number of factors:

1. A growing number of patients in haematology clinics which can lead to lengthy waits.
2. To live with a chronic blood condition, patients require education and support, effectively provided by a clinical nurse specialist (CNS).
3. Nurse-led clinics are supported by recent government and nursing policy which encourages new collaborative ways of working across professional boundaries to make effective use of human and other resources (DH, 1999).

It is envisaged that the nurse-led clinic will enable consultant haematologists to see more complex patients, keeping clinics running in a more efficient and timely manner, and that patients will receive continuity of care and high-quality, multi-professional care.

Role of the haematology clinical nurse specialist

The role of the CNS in the clinic includes the following:

- Monitoring the patient's condition in order to maintain disease stability and control. This involves taking a full history, physical assessment, interpreting blood results, and prescribing and management of medication.
- Educating and empowering patients by explaining the illness to them, their carers and families, assisting them to identify signs of deterioration and how to take appropriate action, and promoting increased compliance with medication.
- Psychological and emotional support/holistic care including referral to allied healthcare professionals as appropriate.

Potential advantages

Development of this nursing role improves the quality of the service provided for haemato-oncology patients (Scope of Professional Practice, 2010) and reduces workload pressures on junior and senior doctors.

Improvements anticipated as a result of implementing this service include:

- Provision of a more flexible service for patients with regards to appointments
- Rapid access to services and reduced waiting times
- Patients increasingly able to deal more effectively with health problems
- Patients' holistic needs being met
- A more cost-effective service for the Trust
- CNS professional development.

The CNS has gained specialist experience in patients with MPNs through shadowing the doctors and running the clinic in parallel with the haematology consultant. CPD will be undertaken to increase CNS knowledge in the MPNs and other general haematology conditions and to develop clinical expertise. This will be achieved through the following:

- Attending relevant study days/courses/conferences
- Visits to/observation of specialist clinics at other centres
- Feedback to and from and discussion with medical and nursing colleagues
- Reflection
- Case studies and problem solving
- Professional portfolio
- Completing the extended nurse prescribing course.

Indemnity

Upon approval of this document and following competency assessment of the CNS by the consultant haematologist, the Trust will provide vicarious liability, providing practice is within written protocols. The Royal College of Nursing indemnity insurance will also cover the CNS.

Accountability

The haematology CNS will at all times adhere to the Nursing and Midwifery Council (NMC) Code of Professional Conduct (2010) and be professionally responsible and accountable for his/her own actions. The NMC makes it clear that the ultimate responsibility is upon the practitioner to determine his/her own individual competence and also to be prepared to refuse to undertake a task if he or she feels they are not competent to undertake it. The consultant haematologist will ultimately remain responsible for the medical management of the patient.

Mode of referral to MPN nurse-led clinic

Referral to the nurse-led clinic may be made by the consultant haematologist, associate specialist or specialist trainees working in haematology. The decision for referral to the clinic will be documented in the medical notes and an MPN nurse-led clinic referral form completed and given to the CNS. The haematology secretaries and administrative clerks are informed by the CNS or individual making the referral so that the patient's name is added to the CNS clinic list.

Criteria for patients to be included

- Patients with PV or ET who are stable and asymptomatic on treatment (venesection, hydroxycarbamide, anagrelide or interferon).
- Patients with MPN who require support to manage their disease effectively.
- Patients in whom the disease progresses or who become unstable and therefore require medical intervention will be referred back to the consultant haematology clinic. All patients will be reviewed annually by a doctor for a physical assessment and to assess for hepatosplenomegaly. This can be done jointly in the nurse-led clinic.

Workload

The CNS can independently see a maximum of 10 patients in one clinic session. Time should be given for administrative work. The CNS should also be available to accompany consultants or SpRs in consultations with new or follow-up patients. The CNS should also be able to refer patients to other members of the multidisciplinary team. Some patients will be able to be monitored through a CNS-led telephone clinic.

Location and frequency

The nurse-led MPN clinic is held in the outpatient department. Frequency of the clinic depends on the patient population and catchment/need, but it should be run in parallel with the consultant clinic so that there is a doctor available to provide advice or see the patient and/or to prescribe medication as needed.

Liaising with doctors

In the event that the CNS needs medical advice about a patient or for the prescribing of medication, he/she liaises with a doctor in haematology. If further investigations are needed, this would be done after discussing the patient with the doctor.

Patients will be seen annually by the doctors for a medical review. The CNS will discuss the patient with the consultant haematologist if he/she is concerned about the patient, for example splenomegaly (e.g. early satiety or abdominal distension) etc.

The CNS will discuss all patients after clinic with the consultant in order to provide medical oversight. The CNS dictates a letter to the patient's GP after each consultation and these letters are also co-signed by the patient's consultant.

Medicines management

Many of these patients will be taking some form of treatment such as hydroxycarbamide, interferon, anagrelide or busulfan to control blood counts or symptoms of disease. Dose adjustments may be required according to blood results and clinical history. When the FBC is stable, the interval between appointment times may be increased to a maximum of four months. In this case, a blood test should be done at two months and the results checked by the CNS. The CNS will then call the patient and inform them of any dose adjustments if needed. If the platelet count is less than 200 on two consecutive occasions the CNS can reduce the dose of hydroxycarbamide. If the platelets are above 400 on two or more consecutive occasions the CNS can increase the dose of hydroxycarbamide. These dose adjustments should be considered alongside other blood results such as haemoglobin and neutrophils, etc.

The CNS will give advice on medications only when he/she is confident that he/she can do so with the same competence as a doctor professing to have that skill (Bolan, 1957). Dose adjustments will be communicated to the patient's GP via a letter which will also be co-signed by the patient's consultant.

Venesection

If a venesection is indicated (to keep haematocrit below a specific target), the CNS will liaise with haematology day care.

Documentation

Patient assessments, blood counts and advice given are documented in the medical notes and the electronic patient record. Information is also entered onto a database detailing the patient's demographics and treatment details, which is constantly updated and modified. This is to help with future audits.

Sickness and annual leave cover

When the CNS is on annual leave or study leave, the clinic will be cancelled and patients will be rescheduled. In the event of sickness, the patients will be urgently accommodated into the consultant clinic.

Evaluation

Evaluation is the systemic, objective and critical assessment of the degree to which services fulfil their stated goals. It can be applied to the processes of care, the actual actions and behaviours of the staff giving the care, and the outcomes of care which refers to what is actually achieved in measurable terms. Evaluation of the nurse-led clinic will aim to establish its effectiveness and benefit both to patients and to the delivery and outcomes of care. Such information will inform future service developments and will add to the evidence base regarding nurse-led clinics in general. The following will be evaluated:

1. Patient satisfaction with aspects of care such as waiting times, continuity of care, history taking and assessment, perception of nurses' knowledge and information giving or advice sharing.
2. Impact on service delivery/organisation of services – sources of referral, number of patients seen, impact of waiting times, length of consultation and "what is it about the nursing that enhances care".
3. Impact on nursing such as identification of training needs, impact on other role functions, number of referrals to others, number of prescriptions required, etc.
4. Audit – systematic and critical analysis reviewed against explicit criteria, allowing practice to be modified where indicated:

    a. Appropriate/inappropriate referrals

    b. Accuracy of treatment advice/dose adjustments

    c. DNA rates

    d. Analysis of complaints

References

Department of Health (1999) Making a difference. Strengthening the nursing, midwifery and health visiting contribution to health and health care. DH London.

Nursing and Midwifery Council (2010) *Code of Professional Conduct.* NMC London.

Nursing and Midwifery Council (2010) *The Scope of Professional Practice.* UKCC London.

Referral Form for MPN (PV/ET) Nurse-led Clinic [template]

N.B. Only refer if the patient is on a stable dose of medication and has controlled counts.
If the patient has active medical problems related to MPN, do not refer.

NAME (OR STICKER): _____

HOSPITAL NUMBER: _____

D.O.B: _____

TYPE OF MPN (Please circle): PV ET

DATE OF DIAGNOSIS: _____

HISTORY OF THROMBOTIC OR HAEMORRHAGIC EVENTS:

DIAGNOSTIC INVESTIGATIONS (Please give results):

PRESENTING FBC: HB G/L

PCV

WBC X 10^9/L

PLTS X 10^9/L

MUTATION STATUS:

ABDOMINAL EXAMINATION/ABDOMINAL USS (Give date):

RCM/PV:_____ DATE:_____

BONE MARROW ASPIRATE AND TREPHINE (DATE):

OXYGEN SATURATIONS: _____ BLOOD PRESSURE: _____

OTHER INVESTIGATIONS:

TREATMENT (Circle): HYDROXYUREA ANAGRELIDE INTERFERON

STABLE DOSE:

OTHER ISSUES:

NAME AND SIGNATURE OF REFERRING DOCTOR: _____

DATE OF REFERRAL: _____

Annex 2: Data Requirements

Haematology oncology services are required to submit data to the following nationally mandated datasets for all patients diagnosed with haematological cancers.

The Cancer Outcomes and Services Dataset (COSD)

The core dataset for all tumour types including haematological cancers is mandated from January 2013, and the site-specific dataset is mandated from July 2013. Details of the dataset can be found on the National Cancer Intelligence Network website:
www.ncin.org.uk/collecting_and_using_data/data_collection/cosd.aspx

The local cancer registry will be collating this dataset using Trust data feeds which should include all these items. The feeds are:

- Trust PAS
- Trust pathology
- Trust radiology
- Trust multidisciplinary team (MDT) feed.

In line with the requirements set out in Provider Trust contracts, this data should be submitted within 25 workings days of the end of the month in which the activity took place.

Three groups of haematological cancers are considered stageable by the Registry:

- Lymphomas, using Ann Arbor (or Murphy St Jude for children)
- Myelomas, using ISS
- CLLs, using Rai and Binet

For the purposes of COSD, any other haematological cancers are not counted as stageable.

For CLL both Rai (0-IV) and Binet (A-C), stages need to be recorded and submitted to COSD to be considered "fully staged".

MGUS does not need to be recorded and submitted as is not defined as an invasive tumour.

Systemic Anti-Cancer Therapy dataset (SACT)

Provider Trusts that provide chemotherapy to patients are required to submit data to the SACT dataset. Details of the audit and the dataset requirements are available on the dataset homepage:
www.chemodataset.nhs.uk/home.aspx

Radiotherapy Dataset (RTDS)

Provider Trusts that provide radiotherapy to patients are required to submit data to the RTDS dataset. Details of the audit and the dataset requirements are available on the dataset homepage:
www.ncin.org.uk/collecting_and_using_data/rtds.

Cancer Waiting Times dataset

Trusts are required to submit data to the Cancer Waiting Times dataset, which includes details of all patients who are referred as a 2 week wait (2ww) referral, and all patients who are treated for cancer. Trusts are required to submit this data within 25 working days of the month of either when the patient was first seen for the 2ww target, or when the patient was treated. The Cancer Waiting Times dataset can be found at: www.datadictionary.nhs.uk/data_dictionary/messages/clinical_data_sets/data_sets/national_cancer_waiting_times_monitoring_data_set_fr.asp

Annex 3: Tables and Flowcharts

Table A: European LeukaemiaNet clinico-haematological response criteria in ET (Barosi, *et al*., 2009)

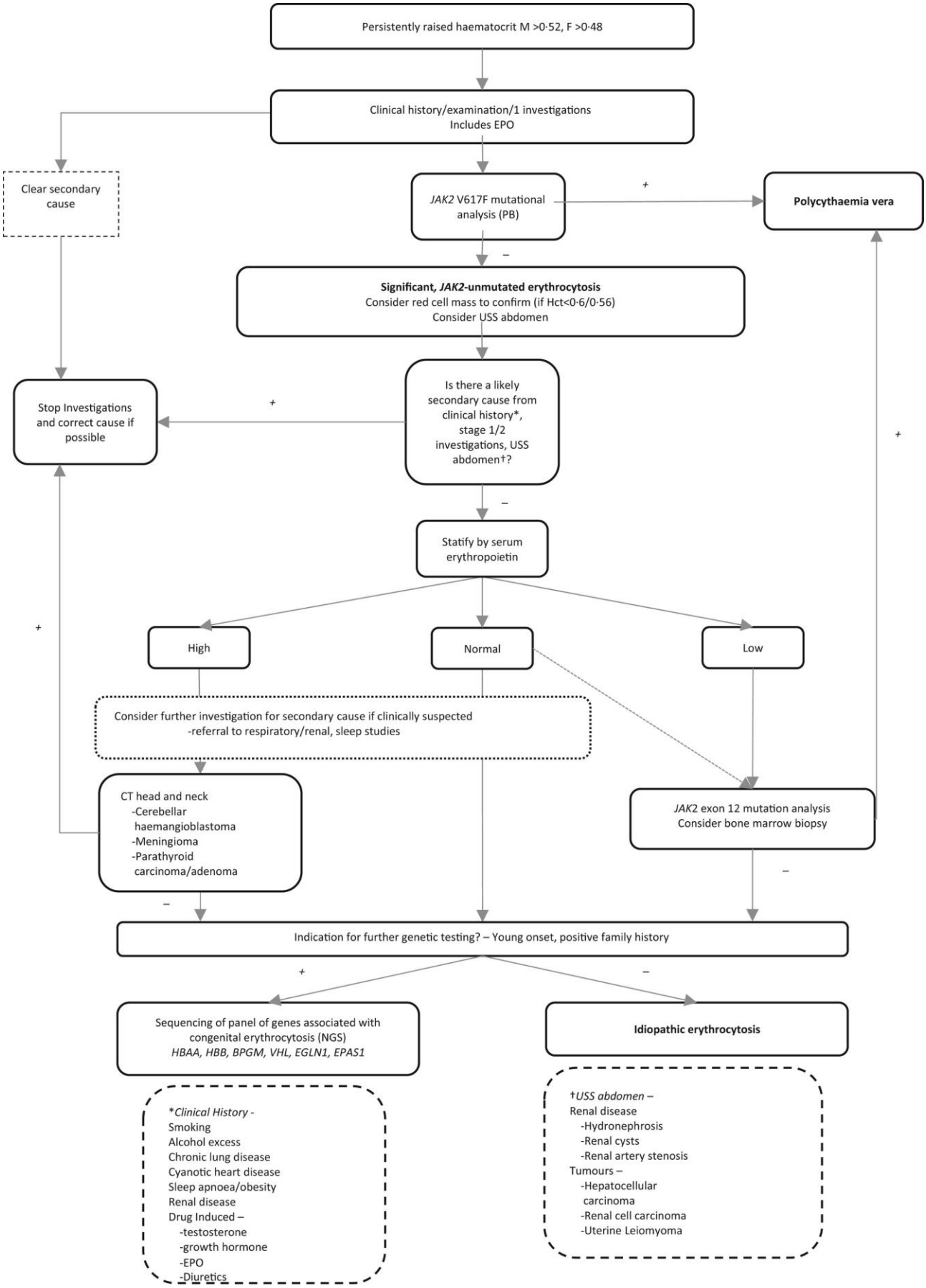
Response grade	**Definition**
Complete response	(1) Platelet count ≤400 × 10^9/L, AND
	(2) No disease-related symptoms, AND
	(3) Normal spleen size on imaging, AND
	(4) White blood cell count ≤10 × 10^9/L
Partial response	In patients who do not fulfil the criteria for complete response, platelet count ≤600 × 10^9/L OR decrease >50% from baseline
No response	Any response that does not satisfy partial response

Table B: Definition of resistance/intolerance to HC in patients with ET (Barosi, *et al*., 2007)

Any one of:

1	Platelet count >600 x 10^9/L after 3 months of maxiumum tolerated dose of HC
2	Platelet count <600 x 10^9/L and WBC less than 2.5 x 10^9/L at any dose of HC
3	Platelet count <600 x 10^9/L and Hb less than 10g/dl at any dose of HC
4	Presence of leg ulcers or other unacceptable muco-cutaneous manifestations at any dose of HC
5	HC-related fever

Flowchart 1: Primary investigations for patients presenting with erythrocytosis (BSH 2018)



Annex 4: Response Criteria and Definition of Resistance

Table A: Definition of clinicohaematological response in PV

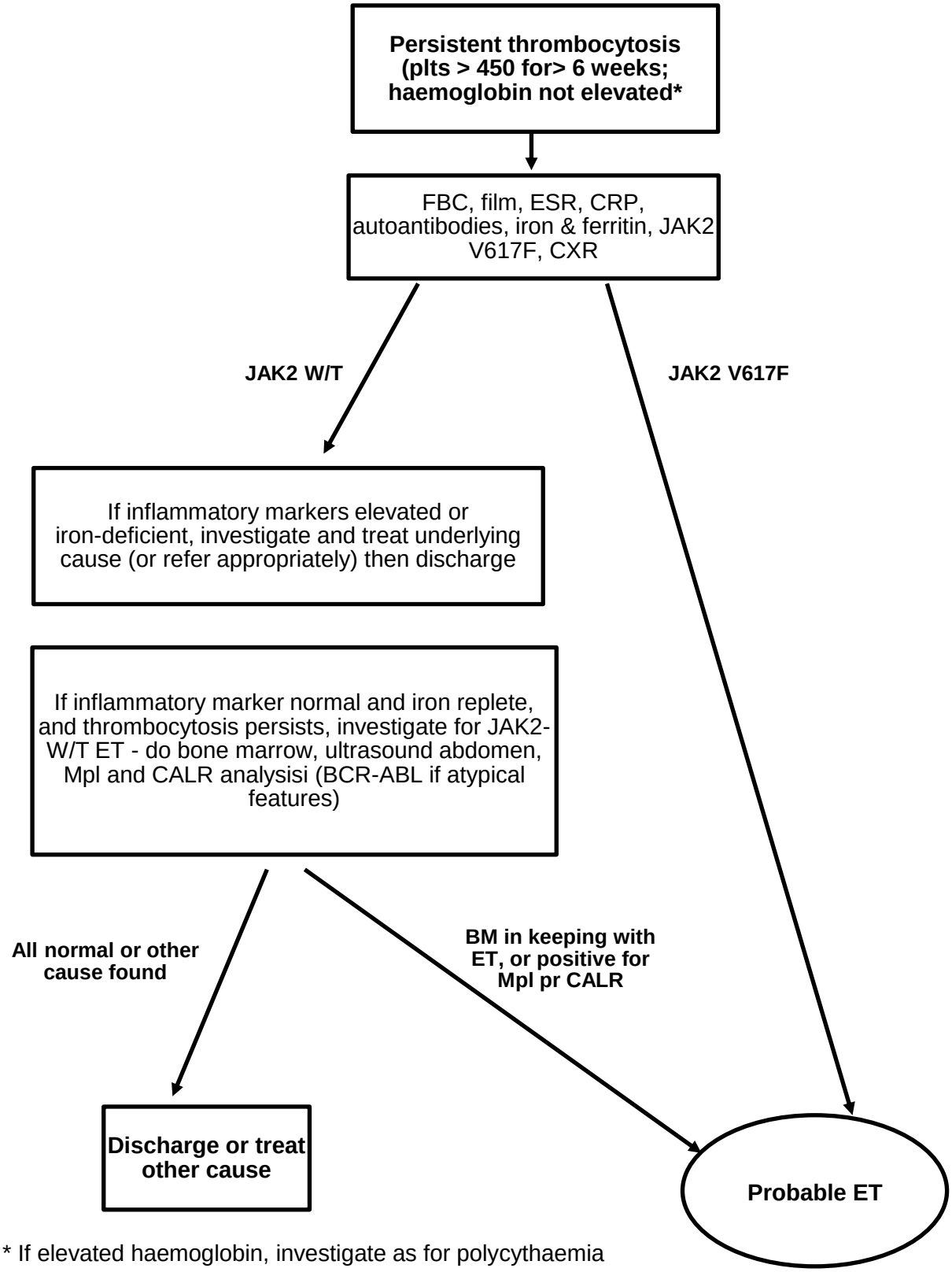
Complete Response (CR)	HCT <0.45 without venesection *and* Platelet count ≤400 x 10^9/L *and* White count ≤10 x 10^9/L *and* Normal spleen size on imaging *and* No disease-related symptoms
Partial Response (PR)	In patients who do not achieve CR, HCT <0.45 without venesection *or* A response in 3 or more of other criteria
No Response	Responses that do not satisfy criteria for PR

Table B: Definition of intolerance/resistance to hydroxycarbamide (HU) in PV

Any of the following:	
1	Need for venesections to keep HCT <0.45 after 3 months of maximum tolerated dose of HU
2	Uncontrolled myeloproliferation, i.e. platelet count >400 x 10^9/L AND white cell count >10 x 10^9/L after 3 months of at maximum tolerated dose of HU
3	Failure to reduce massive splenomegaly by more than 50% as measured by palpation, OR failure to completely relieve symptoms related to splenomegaly, after 3 months of maximum tolerated dose of HU
4	Absolute neutrophil count <1.0 x 10^9/L OR platelet count <100 x 10^9/L OR haemoglobin <10gm/dL at the lowest dose of HU required to achieve a complete or partial clinicohaematological response
5	Presence of leg ulcers or other unacceptable HU-related non-haematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HU.

Flowchart 1: Investigation of patients with persistent thrombocytosis

Patients should be investigated according to the following schema:



* If elevated haemoglobin, investigate as for polycythaemia

Algorithm for management of MPN related SVT

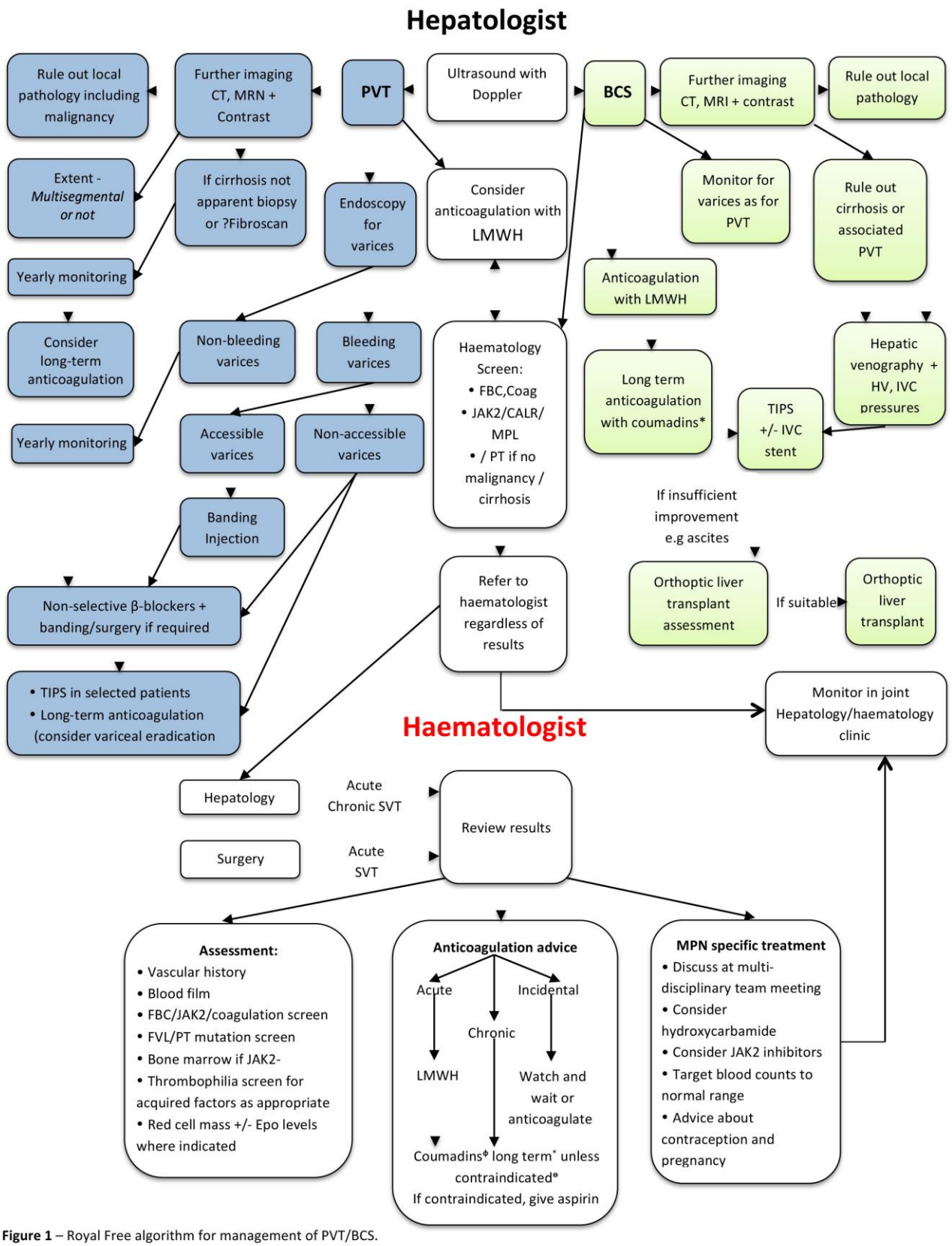


Figure 1 – Royal Free algorithm for management of PVT/BCS.

ᵠ Coumadin monitoring with INR in patients with liver disease may be problematic
˚If persistent risk of thrombosis
ᵠPresence of varices is not a contraindication

PVT-specific management

BCS-specific management

Annex 5: Guide on Dosing/Monitoring Cytoreductive Agents

Hydroxycarbamide (HC)

HC should be commenced at a dose of 500–1000mg daily, increased slowly with the aim of achieving a complete response (CR) or at least a partial response (PR) as defined in Appendix 2.

HC should be avoided in women who are pregnant or lactating, and in patients planning to become pregnant or father children in the near future.

IFNα (pegylated) (e.g. Pegasys)

Pegylated IFNα: it benefits from once-weekly administration and a lower incidence of fatigue, myalgia, etc. As with the non-pegylated form, exercise caution in patients with a history of psychiatric disorders. Usual starting dose 45–90mcg weekly subcutaneously. Doses can be increased slowly up to 180mcg weekly. In some patients, doses less than 90mcg may be required. Prefilled syringes are available as 90mcg, 135mcg or 180mcg (which may be graduated to smaller doses such as 45mcg or 60mcg).

Busulfan

Various dosing regimens exist – see BCSH ET guidelines. Most common dosing regimen is intermittent high-dose busulfan (e.g. 25–40mg every 4–6 weeks).

Busulfan is generally considered to be leukaemogenic (and may cause pulmonary disease) so should be reserved for elderly patients who have failed first-line therapy.

Radioactive phosphorus (^{32}P)

Rarely used, primarily because of its leukaemogenic effect, ^{32}P may be useful for treating selected elderly patients.

Anagrelide

Rarely used in the UK for the management of PV as it is a relatively platelet-specific cytoreductive agent. However, it is known to induce anaemia in some patients and is not considered to be leukaemogenic. So, it may be useful in managing patients who are reluctant to take chemotherapeutic agents such as hydroxycarbamide or busulfan, and who are not adequately managed solely with venesections.

Usual starting dose 500–1000mcg daily, increased slowly to a maximum 10mg daily (max single dose = 2.5mg). Common side effects include palpitations, D&V, headaches, which usually settle after a few weeks. It can occasionally cause serious tachyarrhthmias – request ECG for all patients prior to starting anagrelide and use cautiously in patients with known cardiac disease.

Based on data from trials in ET, anagrelide is associated with a greater risk of progression to secondary myelofibrosis (MF) than is HC, so patients should be counselled appropriately and undergo bone marrow examination every 3 years (or sooner if their blood counts suddenly change). If there is evidence of MF, anagrelide should be stopped and a trial of HC (which may reverse early MF in some cases) considered.

Annex 6: Ruxolitinib: Practical Considerations

Dosing and administration:

*****The recommended initial dosing of ruxolitinib is dependent on the patient's baseline platelet count.

*Certain clinical situations may support initiation of ruxolitinib at a lower dose with subsequent dose adjustments as for (anaemia and neutropenia)

Dose modifications: for insufficient response:

*Increase dose as tolerated, aim for maximum tolerated dose and treat the patient for 6 months before formally assessing response have progressive symptoms or splenomegaly assessed objectively (see table below).

NB: Inadequate reduction in splenomegaly is individual < 50% reduction in palpable splenomegaly may be meaningful & justify continued use of ruxolitinib.

Hematological Toxicities:

*Anaemia and thrombocytopenia usually begin to resolve after the 18th week.

*Thrombocytopenia is managed by dose reduction or if severe, dose interruption (based on clinical parameters). Platelet transfusions may rarely be necessary.

*Anaemia may require blood transfusions and/or dose modifications. Consideration for ESA (NB EPO levels will be high on ruxolitinib), danazol or IMiD such as thalidomide or pomalidomide.

*Severe neutropenia (ANC less than 0.5 X 109/L) is usually reversible on withholding ruxolitinib.

Non-Hematologic Toxicities:

*Increases in lipid parameters can occur. Assess lipids approximately 8–12 weeks following initiation of ruxolitinib. Monitoring and often treatment are required.

*Dose reduction is recommended for patients with moderate (CrCl 30–59 mL/min) or severe renal impairment (CrCl 15–29 mL/min).

*Dose reduction is recommended for patients with any degree of hepatic impairment. See prescribing information.

Infections:

*There is an increased risk of opportunistic infections. Assess for the risk of serious bacterial, mycobacterial, fungal, and viral infections pre-treatment i.e. screen for hepatitis B, C, HIV and if appropriate TB.

*If a patient develops an infection during ruxolitinib therapy it is important where possible to avoid stopping the agent.

*Tuberculosis infection has been reported in patients receiving ruxolitinib and those at higher risk should be tested for latent infection.

*All patients should be tested for hepatitis B and C before treatment. Patients with chronic HBV infection should be treated and monitored.

*Patients with suspected HZV infection should be treated according to clinical guidelines, consider long term prophylaxis.

*Progressive multifocal leukoencephalopathy (PML) – if suspected, ruxolitinib should be discontinued and expert advice sought.

Non-Melanoma Skin Cancer (NMSC):

*Basal, squamous cell, and Merkel cell carcinoma have occurred.

*Perform periodic skin examinations and warn patients about sun exposure.

*Patients with pre-existing Non Melanoma Skin Cancer (NMSC) or previous conditions e.g. actinic keratosis should be cautioned about risk, sun exposure and periodic skin examination.

Stopping ruxolitinib:

*Abrupt withdrawal of ruxolitinib should be avoided, tapering of the dose and warning the patient about resurgence of symptoms and splenomegaly is preferred.. Steroid cover may be helpful.

Potential Signs of Progression for patients on Ruxolitinib or other JAKi

Feature	Treatment options
Spleen	• Threshold: beyond baseline, ↑ by 5cm, more symptomatic • Optimise dose of ruxolitinib • Switch to alternative JAKi • Consider splenectomy?
Symptoms	• Review cause eg mood disturbance other medications • Optimise dose of ruxolitinib • Alternative treatments eg steroid, antihistamine • Switch to alternative JAKi
More anaemia or thrombocytopenia	• Exclude other cause including drug:drug interaction • Does it need treating • Add EPO, danazol, imid
Leucocytosis	• ? Threshold for treatment • Add hydroxycarbamide
Blasts	• Threshold depends on rate of rise </> 10/15/20% • Expectant, consider adding HMA or rarely AML induction

Annex 7: High-risk Pregnancy

- **Previous venous or arterial thrombosis in mother (whether pregnant or not)**
- **Previous haemorrhage attributed to MPN (whether pregnant or not)***
- **Previous pregnancy complication that may have been caused by a MPN:**
  - Three or more unexplained consecutive spontaneous miscarriages before 10th week gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal abnormalities excluded
  - One or more unexplained deaths of morphologically normal fetus at or beyond 10 weeks gestation
  - One or more premature births of a morphologically normal fetus before 34 weeks gestation because of eclampsia, severe pre-eclampsia or recognized placental insufficiency**
  - A significant ante- or postpartum haemorrhage (requiring red cell transfusion)
- **Platelet count rising to >1500 x 10^9/L prior to pregnancy or during pregnancy***
- **Diabetes mellitus or hypertension requiring treatment**

* Indication for cytoreductive treatment but not LMWH.

** Generally accepted features of placental insufficiency include:

(i) abnormal or non-reassuring fetal surveillance tests

(ii) abnormal Doppler flow velocity wave forms analysis suggestive of fetal hypoxaemia

(iii) oligohydramnios

(iv) post-natal birth weight less than the 10th centile for gestational age

5th Floor Alliance House

12 Caxton Street

London SW1H 0QS