PT-1

A randomised trial to compare Aspirin vs Hydroxyurea/Aspirin in ‘Intermediate Risk’ Primary Thrombocythaemia and Aspirin only with observation in ‘Low Risk’ Primary Thrombocythaemia

ISRCTN no: 72251782
EudraCT No: 2004-000245-38
MREC Ref: 97/01/04

TRIAL PROTOCOL VERSION 5.0
1 July 2012

FOR REFERENCE ONLY
IT IS THE USERS RESPONSIBILITY TO ENSURE THIS IS THE CURRENT PROTOCOL BEFORE REFERRING TO
Clinical Study Protocol

Protocol Number: ISRCTN no: 72251782
Protocol code: PT1

EudraCT Number: 2004-000245-38
TGA Reference: 2005/615

Study Title: Primary Thrombocythaemia 1 (amended) Trial - A randomised trial to compare Aspirin versus Hydroxyurea/Aspirin in ‘Intermediate Risk’ Primary Thrombocythaemia and Aspirin only with observation In ‘Low Risk’ Primary Thrombocythaemia

Investigational Product: Hydroxyurea (also called Hydroxycarbamide)
Protocol Version: 5.0

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Study Location: UK & NI, Australia, France, and New Zealand
### Document History

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<td>- Change to wording in protocol and PIS on intermediate risk arm closing to recruitment + continuation of low risk arm recruitment for a further two years</td>
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Investigator’s Agreement

I have read the attached protocol entitled ‘Primary Thrombocythaemia 1 (amended) Trial - A randomised trial to compare Aspirin versus Hydroxyurea/ Aspirin in ‘Intermediate Risk’ Primary Thrombocythaemia and Aspirin only with observation in ‘Low Risk’ Primary Thrombocythaemia’, dated 1 July 2012 and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice the European Clinical Trial Directive (2001/20/EC).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of University of Cambridge and Cambridge University Hospitals NHS Foundation Trust.

PI Signature: ___________________________________________

PI Name (printed): ___________________________  
Date: ___________________
## 1. Study Synopsis

<table>
<thead>
<tr>
<th>Title of clinical trial</th>
<th>Primary Thrombocythaemia 1 (amended) Trial</th>
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<tbody>
<tr>
<td>Main Sponsor name</td>
<td>University of Cambridge and Cambridge University Hospitals NHS Foundation Trust</td>
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<tr>
<td>Eudract number for trial</td>
<td>2004-000245-38</td>
</tr>
<tr>
<td>Medical condition or disease under investigation</td>
<td>Primary Thrombocythaemia (PT) (also called Essential Thrombocythaemia (ET))</td>
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<tr>
<td>Purpose of clinical trial</td>
<td>To collect long term data on patients with PT to assess best treatment and the risk of the disease associated events and transformation</td>
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| Primary objective       | 1) To assess the incidence of thrombosis and major haemorrhage while receiving Aspirin in low risk patients.  
2) To assess if use of Hydroxyurea (also known as hydroxycarbamide) in intermediate risk patients reduces the number of thromboses and major haemorrhage events when added to aspirin  
3) What is the effect of the treatment modalities on quality of life?  
4) High risk patients were initially randomised and some treated with anagrelide. Collection of data to continue to assess the incidence of thrombosis and major haemorrhage long term. |
| Secondary objective(s) | To assess if treatment modality in intermediate risk patients alters the risk of leukaemic or myelofibrotic transformation. |
| Study Design            | Open label phase III study, with 3 groups of patients; low, intermediate and high. Both the high and intermediate risk groups were randomised but have been closed to recruitment. |
| Study Endpoints         | Primary endpoint  
1) The composite primary endpoints for the study are the time from randomisation to thrombosis or haemorrhage event as discussed below:  
   a) Thrombotic Events  
      - New or recurrent myocardial infarction;  
      - Stroke;  
      - Transient cerebral ischaemic attack (TIA);  
      - Deep vein thrombosis;  
      - Pulmonary embolism; |
Secondary endpoints

1) Diagnostic and prognostic value of trephine histology
2) Efficacy of treatment as shown by platelet count control
3) Patient survival
4) Transformation to:
   - Acute leukaemia
   - Myelodysplasia
   - Polycythaemia
   - Myelofibrosis
5) Quality of Life

Sample Size

Low risk group: approximately 280
Intermediate risk group: 560
High risk group: 809

Summary of eligibility criteria

Inclusion criteria:
Patient is 18 years and over
Patient has been diagnosed with PT as defined by:
Platelet count > 600 x 10^9/l
No evidence of overt polycythaemia or of polycythaemia masked by co-existent iron deficiency
No Philadelphia chromosome
Absence of peripheral blood and/or marrow appearances of myelodysplasia or myelofibrosis
No known cause of reactive thrombocytosis
Adequate contraception use

Exclusion criteria:
Patient is pregnant or lactating
The patient is of intermediate risk but has leg ulcers

Following closure of the intermediate and high risk groups to further recruitment the following high and intermediate risk features...
are not eligible in new patients:
Age ≥ 40 years
Platelet count ≥ 1500 x 10^9/l (current or previous)
History of ischaemia, thrombosis or embolic events (including erythromelalgia)
Presence of hypertension or diabetes (which require treatment)
Haemorrhage considered related to ET
Thrombosis considered related to ET

**Investigational medicinal product and dosage**
Aspirin is standard therapy used in all patients (unless patient is intolerant to this in which case substitution of alternative is permitted)

**Active comparator product(s)**
N/A

**Route of administration**
Oral

**Maximum duration of treatment of a subject**
To reflect standard care there is currently no maximum set period for the duration of patients with these treatments. Follow up is advisory to ensure the continuing health of the patients.

**Procedures: Screening & enrolment**
Patients should give informed consent and conform to the inclusion and exclusion criteria.

**Baseline**
Prior to registration the following procedures must be performed for all eligible patients and appropriately recorded into the source notes.
- Medical history, including details of previous treatments (if applicable), pregnancy and smoking
- Physical examination
- Splenic size by clinical examination and, if possible, maximum length by ultrasound examination.
- FBC PCV MCV Film
- RCM if PCV >0.51 males or >0.48 females or if PCV high normal in patients with palpable splenomegaly.
- ESR or plasma viscosity or CRP
- Biochemistry screen (LFT, renal function and urate)
- ECG
It is also recommended that the following procedures are also performed:

- Marrow aspirate and trephine for cytogenetics, morphology and iron stores and blood for research archive and to exclude patients with PV and MF. For previously diagnosed and treated patients who have had cytogenetics performed prior to that therapy it would be helpful but not mandatory to repeat the cytogenetic study on entry to the study.
- 1 peripheral blood film and 9 unstained slides of the trephine biopsy for research into morphology and histological
- 3mls of marrow aspirate in cytogenetic medium or preservative-free heparin for future research into the molecular and genetic pathogenesis of the MPDs.

**Visit 1 Assessment**

**Following randomisation:**
- Equipment will be supplied on trial registration for 10ml of blood to be collected into three tubes for DNA and serum archive and sent to Strangeways Laboratory.

**Routine Assessments**

- Full blood count with differentials.
- Patient evaluation including spleen measurement, if required.
- Patients should be questioned regarding adverse events and medication taken since their last visit and the information captured in the source data.

To assess the diagnostic and prognostic value of trephine histology and to study disease progression to myelofibrosis a repeat bone marrow trephine biopsy, should be taken, ideally at intervals of 3 years.

To monitor the natural progression of the disease and molecular changes over time, annual follow-up blood samples and buccal swabs will be requested.

**Procedures for safety monitoring during trial**

All adverse events will continue to be collected on an annual basis.
| Criteria for withdrawal of patients on safety grounds | If the platelet count cannot be reduced to a level less than 600x10^9/l without producing significant neutropenia, the patient is a ‘treatment failure’, is off protocol and should be recorded as such. Alternatively the patient may be removed from the trial medication for medical reasons if the investigator feels it is in the patient’s best interest, but such patients would remain in the trial for the purposes of obtaining follow-up data, samples and analysis. |

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*Protocol Short title: PT1  Version Number: 5.0  Version Date: 1 July 2012*
## 2. Glossary

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<td>AE</td>
<td>Adverse Event</td>
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<td>ALLG</td>
<td>Australian Leukaemia and Lymphoma Group</td>
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<td>AR</td>
<td>Adverse Reaction</td>
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<tr>
<td>CI</td>
<td>Chief Investigator</td>
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<td>CA</td>
<td>Competent Authority</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>CSR</td>
<td>Clinical Study Report</td>
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<tr>
<td>CTA</td>
<td>Clinical Trial Authorisation</td>
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<td>Cambridge Cancer Trials Centre</td>
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<td>DMC</td>
<td>Data Monitoring Committee</td>
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<td>ESR</td>
<td>Erythrocyte Sedimentation Rate</td>
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<td>ET</td>
<td>Essential Thromocythaemia</td>
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<tr>
<td>FBC</td>
<td>Full blood count</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<td>ISF</td>
<td>Investigator Site File</td>
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<td>ITT</td>
<td>Intent to Treat</td>
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<td>MF</td>
<td>Myelofibrosis</td>
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<tr>
<td>m.g.</td>
<td>Milligram</td>
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<tr>
<td>NAP</td>
<td>Neutrophil Activating Peptide</td>
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<tr>
<td>NCRI</td>
<td>National Cancer Research Institute</td>
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<td>NIMP</td>
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<td>Once daily</td>
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<td>PCV</td>
<td>Packed Cell Volume</td>
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<td>WBC</td>
<td>White Blood Cell</td>
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3. Contact List

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Laboratory Samples

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  University Of Cambridge
  Cambridge Institute for Medical Research
  Wellcome Trust/MRC Building
  Hills Road
  Cambridge
  CB2 0XY

- Bone Marrow Aspirates
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  Hills Road
  Cambridge
  CB2 0QQ
  Email: anthony.bench@addenbrookes.nhs.uk

- DNA Analysis - UK
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- DNA Analysis - France
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*This protocol was originally formulated by the UK Myeloproliferative Disorder Study Group:

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5. Introduction

5.1 Background

The myeloproliferative disease primary thrombocythaemia (PT), also known as essential thrombocythaemia, has a median age of presentation of 60 years but is increasingly being recognised at an earlier age. The risks of the untreated condition are micro-vascular and major vessel occlusive events and haemorrhage. Older patients and those with a previous thrombosis are particularly prone to experience a significant vascular occlusive event. An anti-aggregating agent, such as aspirin, has been shown to reduce/ alleviate minor ischaemic symptoms. Therefore, except in patients with haemorrhagic symptoms, peptic ulceration and known side-effects to aspirin, the use of low-dose aspirin is appropriate.

Myelofibrotic and acute leukaemic transformations can be long-term complications of PT. The ability of therapeutic agents to delay myelofibrosis or reduce/increase the incidence of acute leukaemia in prospective studies is unknown. However, examination of retrospective data provides anxiety about the leukaemogenic risk of the commonly used cytoreductive agent, hydroxyurea. From an analysis of a few relatively small studies of primary thrombocythaemia, the incidence of acute leukaemic transformation in selected patients treated with hydroxyurea has been given as 5-10% over 4-11 years. Based on the risk factors for vascular occlusion, older patients with a thrombotic history and high platelet count can be separated into a 'high' risk group. There is evidence from a randomised prospective study of 'high-risk' patients that cytoreduction with hydroxyurea significantly reduces vascular occlusion. The observed reduction in this prospective study of 29 months median duration was from 24% for those not given cytoreductive treatment to 3.6% for those receiving hydroxyurea — approximately a six-fold reduction. In another prospective study where all patients received hydroxyurea, an incidence of major thrombotic events was 5.6%/year. In these high-risk patients, cytoreductive treatment should therefore be given. The high risk arm of the PT1 trial, which has now closed, assessed the cytoreductive treatment of choice for these high risk patients and the results suggest that hydroxyurea plus aspirin is superior to anagrelide plus aspirin.

In the patients at lower risk of vascular occlusion the dilemma is that the risk of vascular occlusion in untreated patients is relatively low, but includes major life-threatening events. In two small prospective studies of these patients not receiving platelet-lowering agents, the observed major complications were 3% and 4.1% per year and the total complications were 5.1% and 10.5% per year respectively. Cytoreductive treatment should prevent such events and one could predict a similar reduction in complications as seen in the high-risk patients. However, there is evidence that in patients under the age of 40 years the complication rate is only one quarter of that seen in patients aged 40 - 59 years. Therefore it has been decided to divide these patients at lower risk of vascular occlusion into ‘intermediate’ and ‘low risk’ groups. Patients aged 40-59 years will fall into the ‘intermediate risk’ group. This group has now closed to recruitment and was randomised to receive cytoreduction or not, while all will receive aspirin. Patients under 40 years will form the ‘low-risk’ group and will receive aspirin alone. Cytoreductive treatment might also delay myelofibrotic transformation as observed in primary
polycythaemia. However, this benefit and the possible reduction in vaso-occlusive episodes need to be balanced against the potential long-term risk of increasing acute leukaemic transformation.

5.2 Clinical Data

5.2.1 Efficacy

Aspirin was first marketed in 1899 and will be taken by all patients in the study. Aspirin (acetylsalicylic acid) works by stopping platelets forming clots and is extensively used worldwide in patients of high risk of strokes and heart attacks. It has been shown to reduce risks of these events in conditions closely related to PT.

Hydroxyurea (or hydroxycarbamide) is an antineoplastic drug commonly used to treat haematological malignancies. A clinical response should be seen in six weeks.

5.2.2 Safety and tolerability

Aspirin and Hydroxyurea are marketed products and widely used. Adverse drug reactions can be found in section 12.2 - Expected adverse drug reactions, however some of the more common effects are briefly discussed below.

The most common unwanted effect for Aspirin is indigestion and heartburn, and so it should not be used in someone who has a peptic ulcer or has had one in the past. Patients with Asthma should also be carefully considered as aspirin has been linked with asthma attacks. Although rare, renal failure can develop in some patients. In this patient population where patients have increased levels of platelet counts, aspirin can also cause an increase in bruising and bleeding.

A serious side effect of Hydroxyurea can be cytopenia, especially neutropenia, anaemia or thrombocytopenia. Neutropenia can predispose to life threatening infections and patients should be advised of procedures in case of fever.

Some common side effects of hydroxyurea include tiredness, mouth ulcers, headaches and GI upsets such as nausea, diarrhoea or constipation. Rarely there might be skin rashes, or kidney problems.

If hydroxyurea is taken for a long time there can be redness, scaling or increased pigmentation of skin, or thinning of skin or nails in some people. Rarely single cases squamous cell carcinomas have been reported. Leg ulcers are a frequent complication and may necessitate cessation of the drug.

There has been some controversy about whether hydroxyurea increases the risk of PT transforming into acute leukaemia in the long term (if taken for more than 10 years). This question has not yet been answered although from anecdotal evidence any increase in risk is thought to be small (≤ 2 - 5% at 10 years).
Hydroxyurea is renally excreted and should be used with caution in patients with a medical history of renal dysfunction. Caution should also be exercised in patients with hepatic dysfunction.

5.2.3 Pharmacokinetics & pharmacodynamics

5.2.3.1 Hydroxyurea (or hydroxycarbamide)

The exact mechanism of hydroxyurea is unknown. The most important effect appears to be the blocking of the ribonucleotide reductase system resulting in inhibition of DNA synthesis. Cellular resistance is usually caused by increased ribonucleotide reductase levels as a result of gene amplification.\(^6\)

The pharmacokinetic information of hydroxyurea is limited. It is well absorbed and the oral bioavailability is complete. After oral administration maximum plasma concentrations are reached within 0.5 – 2 hours. Hydroxyurea is eliminated partly via renal excretion; however the contribution of this route to the total elimination is unclear. Fractions of the given dose recovered in the urine ranged from 9 – 95%. Metabolism of this has not been thoroughly studied in humans.\(^6\)

5.2.3.2 Aspirin

Aspirin has analgesic, antipyretic and anti-inflammatory actions which are considered to be due to inhibition of the synthesis of prostaglandins. Aspirin also inhibits platelet aggregation by irreversible acetylation of platelet cyclooxygenase.\(^7\)

Absorption of non-ionised aspirin occurs in the stomach and intestine. Some aspirin is hydrolysed to salicylate in the gut wall. After absorption aspirin is rapidly converted to salicylate but during the first 20 minutes following oral administration, aspirin is the predominant form of the drug in the plasma. Aspirin is bound to plasma proteins and is widely distributed. Plasma aspirin concentrations decline rapidly (half life 15-20 minutes) as plasma salicylate concentrations increase. Salicylate is mainly eliminated by hepatic metabolism the metabolites including salicylic acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid and gentisuric acid. As a result of zero order kinetics, plasma steady state salicylate concentrations increase disproportionately with dose. Salicylate is also excreted unchanged in the urine to an extent which depends on the dosage and urinary pH. Renal excretion involves glomerular filtration, active renal tubular secretion and passive tubular reabsorption.

5.2.4 References


6 Trial objective and purpose

This is a NCRI collaborative study in primary thrombocythaemia in adults. By dividing the patients into 3 risk groups this allows the patient population as a whole to be studied during their long term care.

6.1 Primary Objectives

1. In low risk patients (aged 18 to ≤ 39 years): what is the incidence of thrombosis and major haemorrhage while receiving aspirin only?

2. Long term follow up of intermediate risk patients (aged 40 to ≤ 59 years) to observe events associated with disease.

3. What is the effect of the treatment modalities on quality of life?

4. Long term follow up of high risk patients (≥ 60 years) to observe events associated with disease.
6.2. Secondary Objective

1. In intermediate and high risk patients: Does treatment modality alter the risk of leukaemic or myelofibrotic transformation?

2. Assessment of the diagnostic and prognostic value of trephine histology and study of disease progression to myelofibrosis by repeat bone marrow trephine biopsy

3. Best treatment for patients with PT and long term survival of patients.

6.3. Initial study objectives that have been resolved following interim analysis


7 Trial Design

7.1 Statement of design

This is a non-commercial, open label phase III study with three patient groups. The groups are assigned on age and risk factors associated with the PT diseases for forming blood clots. The low risk group are aged 18 to ≤ 39 years with no high risk features. The intermediate group are aged 40 to ≤ 59 years with no high risk features and the high risk group have either high risk features or are aged ≥ 60 years.

High risks of forming blood clots are defined, for this study, as:
- Platelet count ≥ 1500x10^9/l (current or previous) a
- History of ischaemia, thrombosis or embolic events (including erythromelalgia)
- Haemorrhage considered to be related to PT
- Presence of hypertension b or diabetes c

Notes
(a) In patients with borderline counts the allocation of a patient to a high risk group based on platelet count alone should rely on at least three samples taken on separate occasions over at least 2 months. (b) Hypertension is defined as those patients...
requiring anti-hypertensive therapy. (c) Diabetes is defined as those patients requiring therapy with a hypoglycaemic agent.

Patients in the low risk group are treated as per the standard care for this group on a dose of 75mg o.d. aspirin. An exception to this is in Australia where the standard care is 100mg.

Patients in the intermediate group were randomised on a 1:1 basis to either ‘Hydroxyurea and Aspirin’ or ‘Aspirin alone’. This arm is now closed to recruitment.

The original study design had patients in the high risk group randomised on a 1:1 basis to either ‘Hydroxyurea and Aspirin’ or ‘Anagrelide and Aspirin’. However following interim analysis of the data the ‘anagrelide and aspirin’ arm of this randomisation was found to be inferior and an amendment to the trial was performed to close recruitment to this group and investigators were advised to stop treatment with anagrelide. Patients in this group should therefore now be following an observational treatment of standard care, typically hydroxyurea and aspirin.

As the study is long running and patients may need to change groups reference should also be made to the ‘Change of Treatment’ (section 10.2 Change of Treatment).

7.2 Number of Centres

Centres are based in Australia, France, New Zealand and UK & NI. Due to the frequency of low and intermediate risk patients, the aim is to recruit approximately 280 centres. Centres were opened in Ireland but following introduction of the EU Directive these centres were no longer able to continue as a coordinating investigator for the country was not available.

7.3 Number of Subjects

At the time recruitment closed, 809 patients had been recruited in to the high risk group. The intermediate risk group closed to recruitment in July 2012. The low risk group observational patients will be recruited until the study is completed in April 2014.

7.4 Sample size determination

Based on anecdotal evidence the assumption is made that the primary end point (vascular occlusion or haemorrhage) in patients in the intermediate risk group for patients on aspirin might be expected to occur in the order of 4% per annum, a 50% reduction in complication rate requires a 280 sample size in each arm (at 2p = 0.05, with 80% power). Further details are available in section 13.3 Number of Subjects to be enrolled.
7.5 Randomisation (and blinding)

All patients being entered into the study need to be registered with the CCTC in Cambridge. See section 8.3 Assignment and Registration Number. In the low risk group of patients only Aspirin therapy is allocated. The high and intermediate risk patient groups were initially randomised in a 1:1 basis prior to closure of recruitment.

7.6 Study duration

The study was initiated in 1997 and is expected to run for 17 years until 2014. The trial will continue to collect follow up data on all patients until this time.

7.7 Study endpoints

7.7.1 Primary endpoint

- The composite primary endpoints for the study are the time from randomisation to thrombosis or haemorrhage event. Haemorrhage and Vascular occlusion are discussed below (and in more detail as expected serious adverse events in section 12.3 Expected Serious Adverse Events):

  a) Thrombotic Events
     - New infarction or recurrent myocardial infarction;
     - Stroke;
     - Transient cerebral ischaemic attack (TIA);
     - Deep vein thrombosis;
     - Pulmonary embolism;
     - Thrombotic digital ischaemia;
     - Unstable angina;
     - Other thrombotic events
  
  b) Other Vascular Events
     - Other transient neurological event;
     - Erythromelalgia;
     - Other occlusive event

  c) Haemorrhagic events
     - Major haemorrhage;

  d) Death

- In addition there will be analysis of patient Quality of Life
7.7.2 Secondary endpoint

- Disease progression to myelofibrosis as assessed by the diagnostic and prognostic value of trephine histology
- Patient survival
- Efficacy of treatment as shown by platelet count control (high risk arm only)
- Transformation (as discussed in section 12.3 Expected Serious Adverse Events) to:
  1. Acute leukaemia
  2. Myelodysplasia
  3. Polycythaemia
  4. Myelofibrosis

7.8 Trial treatments

7.8.1 Low risk patient group

Patients that fulfil the low risk inclusion criteria will be treated as per the standard care of the disease. Typically this is 75mg of Aspirin taken orally once a day in tablet form. Exceptions to this include where standards differs, in Australia standard care for the disorder is 100mg Aspirin. If the patient is unable to take aspirin, an alternative anti-platelet treatment will be used. Alternative routine aspirin treatments are dipyridamole 100mg t.d.s or 75mg clopidgrel.

7.8.2 Intermediate risk patient group

Intermediate risk patients were randomised to two treatment groups (i) aspirin alone or (ii) aspirin and hydroxyurea in a 1:1 ratio. Dosage of hydroxyurea will be dependent on patient platelet levels and may be modified as the needs of the patient demands. It is important that dose of hydroxyurea is recorded in the patient notes and on the CRF. Aspirin dosage should again be 75mg o.d. unless standard care dictates otherwise. Patients with a contra-indication to aspirin were still randomised, with any alternative to aspirin to be recorded on the CRFs.

7.8.3 High risk patient group

The high risk patient group was initially randomised on a 1:1 ratio to either ‘aspirin and hydroxyurea’ or ‘aspirin and anagrelide’. However following interim analysis by MRC data monitoring committee in 2003, a substantial amendment was written and Investigators were advised to remove patients from anagrelide treatment. This was due to a significantly increased number of adverse events. It was recommended that high risk patients be converted to aspirin and hydroxyurea treatment. Further details can be found in Harrison, Campbell et al, N Engl J Med 2005; 353: 33-45 (Appendix III).
7.9 Criteria for Discontinuation

7.9.1 Individual subject

Patients may be removed from the trial for medical reasons if the investigator feels it is in the patient’s best interest or at the patient’s request. Patients have the right to withdraw for any reason without affecting the standard of care. Unless a patient formally withdraws their consent, all patients who come off trial treatment will remain in the trial for the purposes of follow-up data, analysis, and samples, which should continue to be returned as per the protocol.

7.9.2 Trial

If additional safety information becomes available or new medications for the treatment of PT were marketed then the trial will be reviewed as appropriate.

8 Selection and withdrawal of subjects

For entry into the study the following criteria must be met.

8.1 Inclusion Criteria

To be included in the study the patient must have:

- Given written informed consent
- Aged ≥ 18 years

Patients with PT are eligible assuming they meet the diagnostic criteria as specified below. This includes previously diagnosed patients whether or not they have received treatment and newly diagnosed patients.

- The diagnostic criteria for primary thrombocythaemia for the purposes of this study are:-

1. Platelet count >600x10^9/l.
2. No evidence of overt polycythaemia (confirmed by RCM if necessary) or of polycythaemia masked by co-existent iron deficiency.
4. Absence of peripheral blood and/or marrow appearances of myelodysplasia, or myelofibrosis.
5. No known cause of reactive thrombocytosis. Particular care should be taken to exclude iron deficiency in pre-menopausal women.

Notes:

* In asymptomatic patients, the platelet count should be observed for a period of at least 2 months to confirm >600x10^9/l, and to allow any cause of reactive thrombocytosis to become overt.
† If the PCV is above normal upper limit (that is, males >0.51, females >0.48) or in high normal range in a patient with palpable splenomegaly measure RCM. Iron deficient primary polycythaemia (polycythaemia vera) is strongly suggested if Hb/PCV is normal in the presence of iron deficient red cell changes. In this situation, iron therapy is potentially dangerous.

≠ Exceeding rarely, bcr-abl positive, Philadelphia chromosome negative patients present with high platelet counts and little or no elevation in WBC counts. The features that suggest it is necessary to examine for bcr-abl, are: - basophilia, left-shift in WBC, granulocyte count >16x10⁹/l, difficulty in controlling platelet count, megakaryocytes of low ploidy (NAP is usually unhelpful).

$ A normal ESR, CRP or plasma viscosity is useful in excluding a reactive thrombocytosis.

It should be noted that patients with impaired hepatic / renal function are not excluded although the respective biochemical tests should be monitored during therapy and reduced doses of cytoreductive agent should be used, particularly in the case of hydroxyurea and renal dysfunction.

In instances where the Investigator is unsure of diagnosis the investigator is encouraged to discuss the criteria on a patient by patient basis with the Chief Investigator.

8.2 Exclusion Criteria

The presence of any of the following will preclude patient inclusion from trial entry:

- Medical or psychiatric conditions which may affect the patient’s ability to give consent.

- Any medical or psychiatric condition which in the opinion of the investigator may make it undesirable for the patient to enter the study.

Closure of the intermediate and high risk groups to further recruitment therefore excludes patients with the following features

- High risk features (any of the following)
  - Age ≥ 40 years
  - Platelet count ≥ 1500x10⁹/l (current or previous) a
  - History of ischaemia, thrombosis or embolic events (including erythromelalgia) b
  - Haemorrhage considered to be related to PT b
  - Presence of hypertension c or diabetes d
Notes on the definition of high risk

a. In patients with borderline counts the allocation of a patient to a high risk group based on platelet count alone should rely on at least three samples taken on separate occasions over at least 2 months.
b. Documentation of previous thrombo-embolic, ischaemic and haemorrhagic events should be given on the patient’s entry proforma.
c. Hypertension is defined as those patients requiring anti hypertensive therapy.
d. Diabetes is defined as those patients requiring therapy with a hypoglycaemic agent.

8.3 Assignment and Registration Number

All patients will be registered and assigned a patient identifying number (PIN) by the Cambridge Cancer Trials Centre (CCTC).

For a site to enrol a patient into the study and obtain this number they must have the appropriate regulatory and ethical approvals in place to fulfil their country’s requirements; and a signed Participating Site Agreement (PSA) must completed between the site’s Principal Investigator, the site’s R&D department and the Sponsor (or Co-Sponsor). Sites must have received confirmation from the CCTC that they are open to recruitment prior to enrolling a patient.

Once formally open, a site can contact the CCTC for a patient number. At the time of allocation the CCTC will require the following information from the randomising doctor:

- Name of the site’s Principal Investigator and hospital
- Patient’s name or initials (depending on consent), sex and date of birth
- Date of diagnosis
- At entry to study low risk group

The Cambridge Cancer Trials Centre is available between UK office hours of 09:00 and 16:30 Monday to Friday on Tel: +44 (0) 1223 348 450 or outside of these hours by Fax: +44 (0) 1223 348 071. All registration requests must be sent by fax with the required documentation on eligibility criteria. Any requests received outside of standard UK business hours will be dealt with the following business day. Confirmation in writing of patient eligibility is required for auditing purposes. A template registration form and cover sheet will be provided to all sites.

8.4 Subject withdrawal criteria

8.4.1 Withdrawal from Treatment

A patient should be withdrawn from treatment if at any time:
- It is the wish of the patient (or their legally accepted representative) for any reason
- The investigator judges it necessary due to medical reasons
- The patient receives a prohibited therapy or procedure (section 9.8 Concomitant therapy)

If withdrawn from treatment as per protocol, the patient should continue to be examined and followed up as per the trial procedures, with data recorded in the patient’s notes and on the annual follow up forms.

8.4.2 Withdrawal from Trial

A patient should be withdrawn from the trial at any time if:

- It is the wish of the patient (or their legally accepted representative) for any reason. In this case, no further trial data or samples should be taken for the trial during the patient’s routine care.

- The investigator judges it necessary due to medical reasons. In this case, such patients would remain in the trial for the purposes of obtaining follow-up data, samples and analysis.

If withdrawn from the trial the patient’s final trial examination should be recorded in the patient’s notes with the information that the patient is being withdrawn. It should be recorded on the CRF/follow up page that the patient is withdrawn and the CCTC informed.

Where patients are withdrawn from treatment, or the trial, a replacement patient is not considered necessary to complete the overall numbers needed for the trial.

9 Treatment regimens

9.1 Dosage schedules

9.1.1 Aspirin Therapy

A standard dose of 75mg of aspirin (to be taken with food) will be used in all patients, unless standard care dictates otherwise i.e. 100mg being used in Australia.

At this dosage side-effects are very uncommon, however, aspirin may be contraindicated in patients with a history of intolerance to aspirin, PT-associated haemorrhage or recent peptic ulceration. When there is specific intolerance to aspirin, substitute dipyridamole 100mg t.d.s. for aspirin or 75mg clopidgrel. The use of aspirin is not contra-indicated in patients with PT receiving anticoagulant therapy, although concomitant anti-platelet and anticoagulant therapies should be used with caution. With the introduction of aspirin, the platelet count may rise slightly in some patients.
9.1.2 Route of Administration

All medications taken in this study are oral.

9.1.3 Maximum dosage allowed

Aspirin is given as 75mg once daily, unless other standard care treatment overrides this. As aspirin is an over the counter medicine care should be taken to ensure patient understanding and so compliance of the prescribed amount.

9.1.4 Maximum duration of treatment of a subject

Medically there is currently no maximum set period for the duration of patients with these treatments. Follow up is advisory to ensure the continuing health of the patients. Long term use of hydroxyurea may be associated with transformation to leukaemia; however whether this risk relates to the underlying disease or the treatment is currently not known. Therefore patient data should be collected for the duration of the trial unless consent is withdrawn.

9.1.5 Active comparator products

While initially hydroxyurea was being compared to anagrelide for effectiveness in high risk patients, this comparison was ended following review of the data in 2003.

9.1.6 Procedures for monitoring subject compliance

Patients will be queried during their routine clinic visits to ensure medications are being taken as prescribed. Full blood count analysis is the best indicator to review medication compliance, as missed medication quickly shows in the blood results through rising platelet counts in particular and as mean cell volume (MCV) increases with hydroxyurea treatment.

9.2 Pregnancy

9.2.1 Treatment schedule during pregnancy

Pregnancy in PT requires careful management. In general low risk patients should continue aspirin and be closely monitored by a haematologist and obstetrician. A summary of the literature for pregnancy in PT, is available on request from the trial coordinator.

9.2.2 Pregnancy survey in PT1 patients

Previously an add-on survey of pregnancy in PT has been part of the study with a separate protocol, patient information sheet and consent form. This has been a non-
interventional survey to collect data on patients with PT who become pregnant or with history of pregnancy.

Following discussions, this survey on PT patient pregnancies will be removed from the PT1 trial and will be run as a separate study that will cover all MPD patients. For patients who have already consented for their data to be collected and are still within their pregnancy their data should continue to be collected and submitted to Claire Harrison until after the baby’s birth.

Details of the revised pregnancy survey can be found on request from the trial coordinator.

9.3 Dosage modifications

All low risk patients will be given aspirin at the dose of 75mg o.d., with the exception of Australia where the standard dose is 100 mg o.d.

9.4 Presentation of the drug
The medications used in this study are packaged in tablet form as supplied by the manufacturing authorisation holder. Standard stocks are to be used and dispensed as per local standard procedures.

9.5 Known Drug Interactions

9.5.1 Anticoagulants
Aspirin may enhance the effects of anticoagulants and may inhibit the action of uricosurics.

9.6 Legal status of the drug
Aspirin is a registered trademark of Bayer but is widely available over the counter in a generic format. Aspirin is used for the treatment of a number of conditions and for the prevention of transient ischaemic attacks, strokes, heart attacks, and cancer.

9.7 Drug storage, supply and labelling

9.7.1 Drug Supply
Drugs should be sourced locally and dispensed according to the participating hospital’s locally defined policy.
9.7.2 Drug Storage

Drugs should be maintained as per the manufacturer’s instructions. Typically this is at standard room temperature (25°C). No special precautions are required to maintain drug integrity.

9.7.3 Drug Labelling

As from version 2.0 of this protocol (dated 8 January 2008), trial medications should be labelled in accordance with local hospital policy and country requirements for trial medications. Adherence to the Annex 13 of the Good Manufacturing Practice (GMP) guidelines is not required for this trial. Further details of this exemption can be obtained from the trial coordinator.

9.8 Concomitant therapy

Patients should continue to follow their routine care medications and concomitant medications should be given as per local practice, with the following exceptions.

9.8.1 Aspirin containing medications

Every care must be taken to avoid medications containing aspirin so as not to increase the patient’s dose to overdose levels and also affect the data integrity.

9.8.2 Anticoagulants

With reference to section 9.1 Dosage schedules; Aspirin may enhance the effects of anticoagulants and may inhibit the action of uricosurics.

9.8.3 Other antineoplastic drugs or irradiation

Care should be taken in patients that have previous therapy with antineoplastic drugs or irradiation, if they are of intermediate risk and randomised to hydroxyurea. Adverse reactions are thought to occur more frequently and more severely than if using hydroxyurea alone. Such cases can be discussed with the Chief Investigator if further advice is required.

10 Study procedure and assessments

10.1 Study Assessments

The following procedures will be followed:

10.1.1 Informed consent

When patients are identified that might be suitable for the study they should be approached and given sufficient time to read the patient information sheet and ask
questions regarding the study, as per GCP Guidelines. Before any study specific procedures are performed the patient must consent in writing on the current informed consent form.

Should new information become available during the study the Patient Information Sheet (PIS) may be updated. If the PIS changes all affected patients must be re-consented at the next opportunity.

In addition to the study informed consent form there is an additional sample consent form that the patient is requested to sign, to ensure the samples taken can be used in this study and for future research in to the causes of PT. All samples must be accompanied by a consent form to comply with The Human Tissue Act 2004.

10.1.2 Screening evaluation

Patient eligibility will be assessed using the inclusion and exclusion criteria in section 8.1 Inclusion Criteria and 8.2 Exclusion Criteria.

10.1.3 Baseline data

Prior to registration the following procedures must be performed for all eligible patients and appropriately recorded into the source notes.

- Medical history, including details of previous treatments (if applicable), pregnancy and smoking
- Physical examination
- Splenic size by clinical examination and, if possible, maximum length by ultrasound examination.
- FBC PCV MCV Film
- RCM if PCV >0.51 males or >0.48 females or if PCV high normal in patients with palpable splenomegaly.
- JAK2 mutation status
- ESR or plasma viscosity or CRP
- Biochemistry screen (LFT, renal function and urate)
- ECG

It is also recommended that the following procedures are also performed:

- Marrow aspirate and trephine for cytogenetics, morphology and iron stores and blood for research archive and to exclude patients with PV and MF. For previously diagnosed and treated patients who have had cytogenetics performed prior to that therapy it would be helpful but not mandatory to repeat the cytogenetic study on entry to the study.
- 1 peripheral blood film and 9 unstained slides of the trephine biopsy for research into morphology and histological features of ET should be sent to Professor Tony Green (PT1 Trial), Department of Haematology, Cambridge Institute for Medical Research, Hills Road, Cambridge CB2 0XY.
• 3mls of marrow aspirate in cytogenetic medium or preservative-free heparin for future research into the molecular and genetic pathogenesis of the MPDs by 1st class post to Dr Anthony Bench, Department of Haematology, Box 234 Addenbrookes Hospital, Hills Road, Cambridge, CB2 0QQ.

Once baseline assessments have been performed and patients are confirmed as eligible for the study, the CCTC can be contacted for a patient identifying number (section 8.3 Assignment and Registration Number).

10.1.3.1 Transport of samples

Slides and samples must be transported in such a way to ensure health and safety is maintained during postage.

Where the anticipated postal time is more then 3 days the blood and marrow aspirate samples should be couriered to ensure sample integrity.

Samples sent through the post should comply with current guidance of the basic triple packaging system. (Guidance on regulations for the Transport of Infectious Substances 2005 WHO/CDS/CSR/LYO/2005.22) The system consists of three layers as follows.

1. Primary receptacle. - A labelled primary watertight, leak-proof receptacle containing the specimen. The receptacle is wrapped in enough absorbent material to absorb all fluid in case of breakage.
2. Secondary receptacle. - A second durable, watertight, leak-proof receptacle to enclose and protect the primary receptacle(s). Several wrapped primary receptacles may be placed in one secondary receptacle. Sufficient additional absorbent material must be used to cushion multiple primary receptacles.
3. Outer shipping package. - The secondary receptacle is placed in an outer shipping package which protects it and its contents from outside influences such as physical damage and water while in transit.

Specimen data forms, letters and other types of information that identify or describe the specimen and also identify the shipper and receiver should be taped to the outside of the secondary receptacle.

Samples classed as diagnostic specimens may be transported in packaging which meets the packaging instruction (PI)650. The UN specification marking UN3373 is required. Primary receptacles may contain up to 500 mL each, the total volume in the outer package not to exceed 4L.

Labelling of the outer package for the shipment of diagnostic specimens must include the following.

• for air: the shipper’s (sender’s, consignor’s) name, address and telephone number
• for air: the telephone number of a responsible person, knowledgeable about the shipment
• the receiver’s (consignee’s) name, address and telephone number
• for air: the proper shipping name (“BIOLOGICAL SUBSTANCE, CATEGORY B”)  
• temperature storage requirements (optional).

The UN3373 marking is used for shipments of Category B infectious substances.
• Minimum dimension: the width of the line forming the square shall be at least 2 mm, and the letters and numbers shall be at least 6 mm high. For air transport, each side of the square shall have a length of at least 50 mm
• Colour: none specified, provided the mark is displayed on the external surface of the outer packaging on a background of contrasting colour and that it is clearly visible and legible

• For surface transport (by road, rail and sea): no other mark is required
• For all modes of transport: the mark shall be shown but with the following additional information: The words “BIOLOGICAL SUBSTANCE, CATEGORY B” in letters at least 6 mm high shall be displayed adjacent to the mark.

Required shipping documents – these are obtained from the carrier and are fixed to the outer package:
• a packing list / proforma invoice which includes the receiver’s address, the number of packages, detail of contents, weight, value (note: state that there is “no commercial value” as the items are supplied free of charge)
• an airway bill if shipping by air.

An import and/or export permit and/or declaration (if required).

10.1.4 Visit 1 Assessments
Following registration:
• A registration form and CRF pages will be sent to the site
• Equipment will be supplied following registration for 10ml of blood to be collected into three tubes for DNA and serum archive and sent to Sample Reception, CRUK Department of Oncology, Strangeways Research Laboratory, Wors Causeway, Cambridge, CB1 8RN, for processing and storage.

Where possible the blood and bone marrow samples should be collected prior to the start of treatment with Hydroxyurea. Should the patient need to start treatment straight away, the trial samples should be collected as soon as possible after the beginning of therapy.

10.1.5 Routine Assessments
Disease status evaluation of the patient by full blood count with differentials should be performed regularly to monitor the status of the patient and where appropriate the dose of hydroxyurea should be adjusted. This evaluation should also include spleen measurement, if required.
Visit frequency is at the physician’s discretion, however initially, weekly blood counts are advisable although more frequent checks should be performed in patients receiving high initial dosage regimes. Once the dose of therapy has been stabilised, the patient may be seen less frequently. Typically patients should be seen at least every 3 months.

During their clinic visits patients should be questioned regarding adverse events and medication taken since their last visit and the information captured in the source data.

Details of treatment including dosage changes and adverse events should be reported in the CRF following each visit and returned to the CCTC annually.

10.1.6 Annually

A follow up form to collect patient data should be returned to the CCTC annually, summarising the following details from throughout the year:

- patient’s treatment,
- haematological details,
- spleen size,
- significant adverse events and any vascular complication and transformations,

This information will be collected for 5 years after which the information collected on the patient will be minimised to capture:

- current treatment for PT
- blood counts
- spleen size
- date and type of most recent occlusive/haemorrhagic event,
- date and type of haematological transformations;
- date last known to be alive
- date of death.

Where serious adverse events have been reported on the CRF additional clinical data may be requested if clarification is necessary.

A follow-up blood sample and a sample of constitutional DNA (ex: buccal swab, fibroblasts, hair or nails) will be requested from UK patients enrolled in the trial. These samples will be used to assess disease progression and changes in the molecular status. The samples will be stored respectively at Strangeways Research Laboratory and in the Haematological Disorders Sample Bank in Addenbrookes Hospital. A sample consent form will accompany all samples taken.

50mls of peripheral blood will be taken in tubes in order to extract and store DNA, RNA, protein, viable cells, and serum/plasma. This volume is less than that usually requested to establish the diagnosis of a myeloproliferative disorder. The blood tubes will be provided by the co-ordinating centre. Samples will be processed
according to SOP’s provided by the co-ordinating centre. Further details of collection methods are available from the trial coordinator.

10.1.7 Quality of Life Assessment

Those patients in the intermediate and high risk groups had previously been requested to complete a Quality of Life form once a year for the first five years on the trial. We will continue to collect Quality of Life forms on patients being followed up.

10.1.8 Follow Up Assessments – every 3 years

The role of the bone marrow trephine in PT has become more prominent with the importance placed upon this in the WHO diagnostic criteria for PT. It remains unclear whether these are widely applicable and directly relevant to general clinical practice. The PT1 trial provides a unique opportunity to study these issues. Therefore to assess the diagnostic and prognostic value of trephine histology and to study disease progression to myelofibrosis a repeat bone marrow trephine biopsy, should be taken, ideally at intervals of 3 years.

On the basis that this falls outside of routine patient care it should be considered an optional procedure and this information is included in the patient information leaflets.

Should the patient agree to be sampled for a bone marrow trephine biopsy, the following should be sent to Professor Tony Green (PT1 Trial), Department of Haematology, Cambridge Institute for Medical Research, Hills Road, Cambridge CB2 0XY:

- 1 peripheral blood film,
- 3 unstained bone marrow aspirate slides and
- 9 unstained slides of the trephine biopsy

The patient should consent to these samples appropriately and they should be suitably packaged for posting.

10.1.9 Assessment should the patient transform

The molecular lesions underlying transformation of ET to leukaemia or myelofibrosis are poorly understood. It would therefore be useful to establish a bank of tissue samples and DNA for future studies for patients that transform. If the patient consents to sampling by signing the Sample Consent form, please send the following samples and a copy of the consent form appropriately packaged by 1st class post to:

Dr Anthony Bench (PT1 Trial), Department of Haematology, Box 234 Addenbrookes Hospital, Hills Road, Cambridge, CB2 0QQ.
Email: anthony.bench@addenbrookes.nhs.uk

- 10ml blood in EDTA
- 20ml blood in cytogenetic media
- 3mls of marrow aspirate in cytogenetic medium or preservative-free heparin (if performed)

Professor Tony Green (PT1 Trial), Department of Haematology, Cambridge Institute for Medical Research, Hills Road, Cambridge CB2 0XY.

- 3 unstained bone marrow aspirate slides (if performed)
- 9 unstained slides of trephine biopsy (if performed)

10.2 Change of Treatment
Due to the long term nature of the study it is possible that during their enrolment in the trial the patient may move from one risk group to the next. This should be based on the patient’s overall well-being and not on age alone. A patient reaching 40 years of age should be considered for randomisation if appropriate.

If the patient was enrolled into the low risk group and moves from this to the intermediate group, the investigator should discuss with the patient if they would like to be randomised into the intermediate risk group. If the patient consents, the CCTC should be contacted and informed so a randomised treatment can be allocated.

The high risk study group is closed to further entry, so should a patient develop high risk factors, treatment should be discussed with the patient. This may be the treatment the patient has been on, or the treatment may change. If new medication is required and study medication is discontinued, data should continue to be collected on the patient providing they are willing for its continued collection.

Outcome of patient discussion should be documented in the patient notes for transparency, along with details of the new treatment regimen.

10.3 Long Term Follow Up of Patients

Should a patient move region during the study and no longer be able to attend the hospital at which they were registered, it is the responsibility of the registering PI to provide annual follow up data. The exception to this is if the patient transfers to a hospital that is already running the PT1 trial and has appropriate approvals. In this instance if the new site PI is willing and the patient continues to consent, the patient data may be collected directly from the new site.

If the patient transfers to a site without approvals and the registering PI is not able to collect follow up data the patient will be considered ‘lost to follow up’.
In the UK, where a patient consents, they will be flagged with the Office of National Statistics to indicate that they are on a trial. Information of their death can then be included in the trial data.

10.4 DNA Analysis

Since the start of the study in 1997 the importance of molecular biomarkers has risen. Collection of blood and bone marrow samples was written into the original design with the aim to conduct future research. A number of genes have been shown to be of interest since 1997; two of the most predominant of these are the JAK2 and MPL mutations.

This study will involve the investigation of the prevalence of these two genes within the PT1 patient groups as well as aiming to identify targets for future drug therapy and to optimise management of haematological patients through a deeper understanding of the biology of the disease. Samples will remain linked to clinical outcome data, with interest in the patient subgroups and long-term evolution of the disease. At the end of the study samples will be sent to a tissue bank.

It should be noted that results of the analysis will not be available to clinicians on a patient by patient basis as analysis will be performed on a research basis.

11 Evaluation of Results

11.1 Assessment of Efficacy

Efficacy will be assessed by the time to first thrombotic event or major haemorrhage, with subsidiary analyses of cumulative event rates and time to leukaemic transformation or myelofibrosis.

The randomisation data analysis will be stratified by whether the patients treated were newly diagnosed or previously treated. Where there was previous treatment this will include whether or not prior aspirin and/or prior cytoreductive therapy had been given.

All analyses will assume that there may be some quantitative differences in the size of any treatment effects in the different strata, but that there is unlikely to be any qualitative difference (i.e. harm in one group, benefit in another).

The final analysis for differences between the arms in the primary end-point will be performed as an intention-to-treat, time-to-first-event analysis, and will not need to be adjusted for the prior analyses due to the conservative nature of the Haybittle-Peto rule.

Where the patients were not randomised, i.e. treated on aspirin alone, the observational data will be reviewed for complication rates to define the natural history of the disorder.
An independent data monitoring committee will review the data on an annual basis and provide feedback to the Leukaemia Trials Steering Committee (see also section 13.2 Interim analyses).

11.2 Response criteria

11.2.1 Quality of life

Quality of life (QL) will be assessed using the EORTC QLQ-C30 version 2 questionnaire (Appendix II) at randomisation and yearly thereafter for five years. Scoring is according to guidelines provided by the EORTC QL Group with scores interpreted so that increased functional status indicates a benefit whereas increased symptoms indicate a poorer quality of life. A treatment-specific module designed for this trial will be included. In France the EORTC QL-C30 version 3 will be used due to discontinuation of version 2.

11.2.2 Blood Count results

Blood count results will be analysed to document response to therapy. Differences in responses among molecularly and histologically defined subgroups will also be analysed along with the long term evaluation of the disease.

11.2.3 Review of Bone Marrow Slides as prognostic indicators

Slides of bone marrow trephines and aspirates will be reviewed by 3 independent experts – Dr Wendy Erber (Cambridge) Dr David Bareford (Birmingham) and Dr Bridget Wilkins (London) to see if they find markers that could be used to as prognostic indicators.

12 Assessment of Safety

12.1 Definitions

12.1.1 Adverse event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product. Such adverse events should be followed until resolution or until stabilisation.

12.1.1.1 Pre-existing conditions
In this study, a pre-existing condition (i.e. a disorder present before randomisation and noted on the medical history) should not be reported as an adverse event unless the condition worsens.

12.1.1.2 **Study Disease**

Deterioration in the study disease should be reported as an adverse event.

12.1.1.3 **Procedures**

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. A medical condition for which an unscheduled procedure was performed, should however be reported if it meets the definition of an AE. For example the acute appendicitis should be reported as an adverse event rather than the appendectomy.

12.1.2 **Adverse reaction of an investigational medicinal product (AR)**

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship or no other reasonable aetiology.

12.1.3 **Unexpected adverse reaction**

An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SPC) for an authorised product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on patient/event outcome or action criteria.

12.1.4 **Serious adverse event or serious adverse reaction**

Any untoward medical occurrence or effect that:
- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing inpatient hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if
it were more severe.

Suspected unexpected serious adverse reactions (SUSARs) should be notified to the co-clinical lead (Dr Harrison) within 24 hours of the site becoming aware of the event occurring.

12.2 Expected adverse drug reactions

The medications used within the trial have been marketed for some time and consequently the following adverse drug reactions have been observed and reported in the SPCs. Consequently the following adverse reactions need not be reported as Suspected Unexpected Serious Adverse Reaction (SUSAR):

12.2.1 Hydroxyurea

Bone marrow depression is the dose limiting toxicity. Gastrointestinal side effects are common but require rarely dose reduction or cessation of treatment.

- **Common ( >1/100, <1/10)**
  - **Blood:** Bone marrow depression, leucopenia, megaloblastosis.
  - **Gastrointestinal:** Diarrhoea, constipation.

- **Uncommon ( >1/1,000, <1/100)**
  - **Blood:** Thrombocytopenia, anaemia
  - **Body as a whole:** Nausea, vomiting, anorexia, stomatitis. Drug fever, chills, malaise.
  - **Skin:** Maculopapular rash, facial erythema, acral erythema.
  - **Liver:** Elevation of liver enzymes, bilirubin.
  - **Urogenital:** Transient impairment of the renal tubular function accompanied by elevation in serum uric acid, urea and creatinine.

- **Rare: (>1/10,000, <1/1,000)**
  - **Body as a whole:** Hypersensitive reactions
  - **Skin:** Alopecia.
  - **Respiratory:** Acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fever and dyspnoea, allergic alveolitis.
  - **Urogenital:** Dysuria.
  - **Neurological:** Rare neurological disturbances including headache, dizziness, disorientation, hallucinations.

- **Very rare: (<1/10,000)**
  - **Skin:** Dermatomyositis-like skin changes, Hyperpigmentation or atrophy of skin and nails, cutaneous ulcers (especially leg ulcers), Pruritus, actinic keratosis, skin cancer (squamous cell cancer, basal cell carcinoma), violet papules, desquamation.
  - **Urogenital:** renal impairment.

In the therapy with hydroxyurea megaloblastosis may occur which does not respond to treatment with folic acid or B\textsubscript{12}. 
The bone-marrow suppression subsides, however, when therapy is discontinued. Severe gastric distress (nausea, emesis, anorexia) resulting from combined hydroxyurea and irradiation therapy may usually be controlled by temporarily discontinuing hydroxyurea administration.

Hydroxyurea may aggravate the inflammation of mucous membranes secondary to irradiation. It can cause a recall of erythema and hyperpigmentation in previously irradiated tissues. Erythema, atrophy of skin and nails, desquamation, violet papules, alopecia, dermatomyositis-like skin changes, actinic keratosis, skin cancer (squamous cell cancer, basal cell carcinoma), cutaneous ulcers (especially leg ulcers), pruritus and hyperpigmentation of skin and nails have been observed in isolated cases partly after years of long-term daily maintenance therapy with hydroxyurea.

High doses may cause moderate drowsiness.

Rare neurological disturbances including headache, dizziness, disorientation, hallucinations, and convulsions have been reported.

In rare cases dysuria or renal impairment, hypersensitive reactions.

In individual cases allergic alveolitis.

In patients receiving long-term treatment with hydroxyurea for myeloproliferative disorders, such as polycythemia vera and thrombocytopenia, secondary leukemia may develop. To what extent this relates to the underlying disease or to treatment with hydroxyurea is presently unknown.

Hydroxyurea can reduce plasma iron clearance and iron utilisation by erythrocytes. However, it does not appear to alter the red blood cell survival time.

12.2.2 Aspirin

- Dyspepsia, nausea and vomiting.
- Less commonly irritation of the gastrointestinal mucosa may lead to erosion, ulceration and gastrointestinal bleeding. Hepatotoxicity, which occurs rarely.
- Hypersensitivity reactions including urticaria, rhinitis, angioneurotic oedema and severe bronchospasm.
- Aspirin may enhance the effects of anticoagulants and may inhibit the action of uricosurics.
- Aspirin may precipitate bronchospasm and may induce attacks of asthma in susceptible subjects.
- Aspirin may cause salt and water retention as well as deterioration in renal function.

12.3 Expected Serious Adverse Events
Within these patient populations the following serious adverse events are expected and need not be reported as a SUSAR:

12.3.1 **Thrombotic Events**

12.3.1.1 **New infarction or recurrent myocardial infarction**
Myocardial infarction is defined as the presence of two or more of the following criteria:

a) Symptoms of cardiac ischaemia
   - Characteristic ischaemic chest pain in the precordium or associated referral areas, lasting for at least 20 minutes

b) Significant cardiac enzyme elevations
   - Elevation of CK, LDH, or AST to at least twice the upper limit of normal for the given laboratory in the absence of other explanation.

c) ECG changes
   - Occurrence of new 40 msec Q waves in at least two adjacent ECG leads, or development of a new dominant R wave in V1 (R ≥ 1mm >S in V1) or of new ST elevation or depression or persistent (>48 hours) new T wave inversion.

12.3.1.2 **Stroke and stroke type**
A stroke is a new focal neurologic deficit of presumed vascular origin which persists for >24 hours or results in death within 24 hours.

**Stroke type**
- Haemorrhagic: A stroke caused by primary intracranial haemorrhage diagnosed by CT, MRI, or other objective means, or by autopsy.
- Ischaemic: A stroke of atherothrombotic or embolic origin as diagnosed by CT, MRI or other objective means, or by autopsy.
- Uncertain: A stroke not otherwise classified by the above criteria.

12.3.1.3 **Transient cerebral ischaemic attack (TIA)**
A Transient Ischaemic Attack is defined as the abrupt onset of unilateral motor or sensory disturbance, speech defect, homonymous hemianopia, constructional apraxia, or transient monocular blindness (defined as the abrupt onset of unilateral decreased visual acuity involving a portion or the entirety of the visual field) that resolved completely in less than 24 hours.

12.3.1.4 **Deep vein thrombosis**
A deep vein thrombosis (DVT) is defined as a typical clinical picture with positive investigation: i.e. phlebography, ultrasonography, CT in unusual sites. In case of suspected recurrence in a site of previous DVT (e.g.
ipsilateral limb) diagnosis is accepted only if the investigation shows extension or recurrence of thrombosis as compared to a previous test.

12.3.1.5 Pulmonary embolism
A pulmonary embolism is defined as a typical clinical picture with positive angiography or high-probability V/Q scanning.

12.3.1.6 Thrombotic digital ischaemia
This is characterised by purplish discoloration of toes/fingers, which may progress to infarction if untreated. Digital ischaemia may occasionally be associated with erythromelalgia.

12.3.1.7 Unstable angina
In this instance this is defined in accordance with TIMI criteria as presence of prolonged angina or recurrent angina at rest, together with one of the following: new ST segment depression, requirement for revascularization procedure, cardiac enzyme rise to less than twice the upper limit of normal or past history of documented coronary artery disease.

12.3.1.8 Other thrombotic event
Thrombosis in sites not covered above. In particular, characteristic symptoms of peripheral limb ischaemia with evidence of thrombosis. In addition characteristic syndromes of venous thrombosis for example; Budd Chiari syndrome, portal vein thrombosis, retinal vein occlusion, or cerebral sinus thrombosis.

12.3.2 Other Vascular Occlusive Events

12.3.2.1 Other transient neurological event
This is defined as the abrupt onset of poorly or non-localising neurological symptoms such as unsteadiness, blurred vision, hearing disturbance or unstable gait.

12.3.2.2 Erythromelalgia
Erythromelalgia is defined as the onset of pain at the extremities associated with temperature increase and redness of the skin. Erythromelalgia usually manifests in the lower extremities and/or rarely in the hands with frequent recurrences in the same areas.

12.3.2.3 Other occlusive event
Oclusion in sites not covered above. In particular, characteristic symptoms of cardiac, abdominal or peripheral limb ischaemia supported by objective evidence of vessel disease and/or ischaemia.

12.3.3 Haemorrhagic Events
12.3.3.1 **Major haemorrhage**
Overt haemorrhage associated with either a decrease in haemoglobin level of at least 2g/dl or a need for blood transfusion of 2 or more units of blood, or if haemorrhage is retroperitoneal or intracranial.

12.3.3.2 **Minor haemorrhage**
Overt haemorrhage not meeting the criteria of major haemorrhage

12.3.4 **Death**
The cause of death should be given, including ‘post mortem’ findings where possible

12.3.5 **Acute leukaemic transformation.**
Leukaemic transformation may occur abruptly but often suspicious peripheral blood changes occur many months before a marrow sample confirms the transformation. The time of transformation must be taken as the date of the diagnostic marrow sample. Blast cells must comprise >20% of nucleated cells. FAB typing, immunophenotyping and repeat karyotypic analysis should be carried out.

12.3.6 **Myelodysplastic transformation.**
Myelodysplastic transformation is uncommon in PT although cytoreductive treatment might increase its incidence. The usual diagnostic criteria should be used and the marrow karyotype repeated.

12.3.7 **Polycythaemic transformation.**
Very occasionally patients with PT transform into primary polycythaemia. If the PCV rises above 0.51 for males or 0.48 for females measure the RCM. If the measured RCM is more than 25% above the patient’s mean normal predicted value, then the routine investigations for polycythaemia should be performed. In the presence of an absolute polycythaemia without an identifiable secondary cause, the additional finding of a JAK2 mutation would be sufficient for a diagnosis of polycythaemia vera.

In patients lacking a JAK2 mutation, palpable splenomegaly or a marrow cytogenetic abnormality would be sufficient for the diagnosis of polycythaemia vera. In the absence of palpable splenomegaly and with normal cytogenetics, two of the following must additionally be present for the diagnosis: a) platelets >400x10^9/l, b) neutrophils >10x10^9/l c) enlarged spleen on ultrasound scan (>12 cms) d) reduced serum erythropoietin or presence of erythropoietin-independent BFU-e.
12.3.8 Myelofibrotic transformation.

It is often difficult to give a precise time of onset of myelofibrosis. Diagnosis requires the presence of reticulin grade 3 or higher (on a 0-4 scale) and development of any two of the following conditions: (i) palpable splenomegaly, (ii) otherwise unexplained anaemia (haemoglobin < 11.5g/l for men or < 10g/l for women); (iii) teardrop red cells on peripheral blood film; (iv) leucoerythroblastic blood film (presence of at least 2 nucleated red cells or immature myeloid cells in peripheral blood film); (v) systemic symptoms (drenching night sweats, weight loss >10% over 6 months or diffuse bone pain); (vi) histologic evidence of extramedullary hematopoiesis.

12.4 Recording and evaluation of adverse events

Individual adverse events should be evaluated by the investigator and, where indicated, they should be reported to the sponsor for evaluation on the annual follow up form. This includes the evaluation of its seriousness and the causality between the investigational medicinal product(s) and/or concomitant therapy and the adverse event. The sponsor has to keep detailed records of all AEs reported to them by the investigator(s) and to perform an evaluation with respect to seriousness, causality and expectedness.

12.4.1 Assessment of severity

Assessment of severity should be assessed according to The NCI Common Terminology Criteria for Adverse Events v3.0. This is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

It can be found on the following website:

Due to the well known and low risk nature of the medications, adverse events graded as Grade 2 or below need not be reported. All other adverse events should continue to be collected on the CRF pages.

12.4.2 Assessment of causality

Definitely: A causal relationship that can only be the result of the investigational medicinal product and there is no other plausible cause of the AE.

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product.

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible.

Unrelated: A causal relationship can be definitely excluded and another
documented cause of the AE is most plausible.

12.4.3 **Outcome**

The outcome of the event should be recorded. Typically these will include: Resolved; Resolved with sequela; Death; or ongoing if not resolved at the end of the study.

12.5 **Reporting adverse events**

The sponsor is responsible for the prompt notification to all concerned investigator(s), the Research Ethics Committee and competent authority (e.g. MHRA) of each concerned Member State / Country of findings that could adversely affect the health of subjects, impact on the conduct of the trial or alter the competent authority’s authorisation to continue the trial in accordance with Directive 2001/20/EC and other regulations as appropriate.

12.6 **Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)**

All suspected adverse reactions related to an investigational medicinal product (the tested IMP) which occurs in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting.

12.6.1 **Who should report and whom to report to?**

The sponsor, or designee, should report all the relevant safety information previously described to the concerned competent authorities and to the Ethics Committee concerned. The sponsor or designee shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects.

12.6.2 **When to report?**

12.6.2.1 **Fatal or life-threatening SUSARs**

The Sponsor should notify the Competent Authority and the Research Ethics Committee as soon as possible but no later than 7 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting.

In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to the CA and the Ethics Committee within an additional eight calendar days.

12.6.2.2 **Non fatal and non life-threatening SUSARs**

All other SUSARs and safety issues must be reported to the competent authority and the Ethics Committee in the concerned countries as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.
12.6.3 How to report?

12.6.3.1 Minimum criteria for initial expedited reporting of SUSARs
Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted by the Sponsor within the time limits as soon as the minimum following criteria are met:

a) a suspected investigational medicinal product,
b) an identifiable subject (e.g. study subject code number),
c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
d) an identifiable reporting source,
and, when available and applicable:
- an unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number),
- an unique case identification (i.e. sponsor's case identification number).

12.6.3.2 Follow-up reports of SUSARs
In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. The sponsor should report further relevant information after receipt of follow-up reports.

In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

12.6.3.3 Format of the SUSARs reports
Electronic reporting should be the expected method of the Sponsor for expedited reporting of SUSARs to the competent authority. In that case, the format and content as defined by the Guidance of the CA should be adhered to.
The CIOMS-I form is a widely accepted standard for expedited adverse reactions reporting. However, no matter what the form or format used, it is important that the basic information/data elements described in annex 3 of the EU directive or as per country requirement, when available, be included in any expedited report (some items may not be relevant, depending on the circumstances).

13 Statistics

13.1 Statistical methods to be employed
Analyses will be performed using standard contingency table and log-rank methods based on the intention to treat (ITT) — i.e. all patients believed to be eligible at the time of randomisation will be included in the analysis, irrespective of protocol compliance, change of diagnosis, etc. The primary analysis will be of time to first thrombotic event or major haemorrhage, with subsidiary analyses of cumulative event rates and time to leukaemic transformation or myelofibrosis. The randomisation — and data analyses — will be stratified by whether newly diagnosed or previously treated (and, if the latter, by whether or not prior aspirin
and/or prior cytoreductive therapy had been given). All analyses will assume that there may be some quantitative differences in the size of any treatment effects in the different strata, but that there is unlikely to be any qualitative difference (i.e. harm in one group, benefit in another).

The final analysis for differences between the arms in the primary end-point will be performed as an intention-to-treat, time-to-first-event analysis, and will not need to be adjusted for the prior analyses due to the conservative nature of the Haybittle-Peto rule.

13.2 Interim analyses

Interim analyses of the main endpoints will be supplied annually, in strict confidence, to an independent data monitoring committee. In the light of these interim analyses, the data monitoring committee will advise the chairman of the Leukaemia Trials Steering Committee if, in their view, the randomised comparison has provided proof beyond reasonable doubt that for all, or for some types of patient one treatment is clearly indicated or clearly contraindicated. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least 3 standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the trial prematurely (the Haybittle-Peto rule).

Interim analyses will be supplied to the DMEC at least annually, and will include details of the primary and secondary end-point events, as well as any unexpected or serious toxicities arising in the two arms. The DMEC will use the Haybittle-Peto guideline (effect size >3SDs) for early trial closure.

13.3 Number of Subjects to be enrolled

The trial is currently recruiting in the United Kingdom and Northern Ireland, France, Australia and New Zealand.

In the 'intermediate-risk' 40-59 year old study, the primary end-point (thrombosis or major haemorrhage) in the 'aspirin only' arm might be expected to be in the order of 4% per annum. To detect a medically worthwhile 50% reduction in complication rate (at 2p=0.05, with 80% power) the sample size required is 280 in each arm followed for a median of 4 years, assuming a similar complication rate in each year (i.e. cumulative complication rates of 16% versus 8%). If the reduction in complication rate were greater than 50%, then fewer patients would be needed to detect this difference. Patients that drop out will not be replaced.

It was outlined in a progress report to the LTSC (November 2006) that it is believed that the low event rate means that the power calculation should be rephrased in terms of number needed to treat rather than relative risk reduction. That is, if the event rate is very low, then even if there is a true difference between the arms, it may not be of sufficient magnitude to justify the use of hydroxyurea in this age group, particularly with the potential (unproven) risk of leukaemia in the long-term. Without knowing the specific long-term risk of hydroxyurea therapy, it is difficult to know at what threshold the number needed to treat with hydroxyurea would be
too great to justify its routine use. However, it seems reasonable to argue that if the point estimate for the number needed to treat (NNT) to prevent one primary end-point event per year is $>100$, with a lower bound on the $95\%$ confidence interval (CI) of $50$, then aspirin alone would be the therapy of choice.

The intermediate risk arm has now reached the maximum period of time required to generate a significantly different treatment effect or a point estimate for NNT of $>100$, with $95\%$ confidence that NNT $>50$. Therefore, the intermediate risk arm has been closed to recruitment, but patients will continue to be followed up in order to capture any further events that may occur during the follow up period.

13.4 Definition of the end of the trial

The end of the trial will be the date of the last visit of the last patient undergoing the trial. This is estimated to be 30 April 2014.

14 Study Organisation

The Cambridge Cancer Trials Centre (CCTC) is responsible for overseeing the trial conduct and monitoring the study progress, running the study on a day to day basis, centre initiation, and reporting to the Steering Committee.

The study is clinically led by Chief Investigator Professor Anthony Green and Co-Clinical Leads Dr Claire Harrison and Dr Peter Campbell. Included within Dr Harrison’s role is coordination of SUSAR reporting and ethical amendments.

The Cambridge Cancer Trials Centre (CCTC) has responsibility for patient registration, data management, CRF collection, sending of sampling tubes, analysis and presentation of the results, and reporting to the DMC.

Jon van der Walt is responsible for the processing and storage of the bone marrow slides and blood films.

Within the UK, the CRUK Department of Oncology has responsibility for DNA extraction and storage at the Cambridge University Strangeways laboratory.

The DMC and LTSC review the data annually and monitor the study progress, providing trial oversight.

Direction de la Recherché Clinique AP-HP have responsibility for the study in France. They coordinate site selection and ensure appropriate procedures are followed and correspond with the regulatory and ethical committees. The coordinating investigator acting on behalf of the AP-HP is Dr Jean-Jacques Kiladjian.

Within France, Dr Bruno Cassinat, Service de Médecine Nucléaire du Pr. Moretti, has responsibility for DNA extraction, JAK2 testing and sample storage.
The Australian Leukaemia and Lymphoma Group (ALLG) have responsibility for the study in Australia and New Zealand. They coordinate site selection and ensure appropriate procedures are followed and correspond with the regulatory and ethical committees. The coordinating investigator acting on behalf of the ALLG is Dr Cecily Forsyth and day to day activities for the trial are coordinated from the Peter MacCallum Cancer Centre.

14.1 Site Responsibilities

The principal investigator at each participating site has overall responsibility for the study and all patients entered into the study but may delegate responsibility down to other member of the study team as appropriate. The principal investigator must ensure that all staff involved are adequately trained and their duties logged on the Site Responsibilities Sheet.

14.2 Study Start-up and core documents

Centres wanting to participate in the study should contact the CCTC to obtain information. The principal investigator at the centre should have available the following core documents before the site becomes active:

- The site contact details
- Participating site agreement
- A current signed and dated copy of each participating investigators CV
- Site responsibilities sheet
- Ethics approval
- R&D approval

15 Direct access to source data / documents

The investigator must make records available should a competent authority inspection occur or an IRB/IEC requests a review. Although non-commercial in nature should a trial monitoring visit or audit be requested the investigator must make available the trial documentation and source data to the Sponsor representative.

16 Quality Control and Quality Assurance

Checking of the clinical data base occurs as per the CCTC standard procedures.

All adverse event and histological materials are reviewed by the appropriate central clinical and histological committees blinded to PT treatment.
17 Ethical considerations

17.1 Consent
Prior to entry into the trial, patients with PT will be informed about the trial and asked to give written informed consent if willing to participate in the study. A separate consent will be requested for samples to be taken and stored. Before signing the consent the patient should be given sufficient time to consider their participation. A patient may decide to withdraw from the study at any time without prejudice to their future care.

17.2 Ethical committee review
The study protocol is to be seen and approved by the appropriate independent ethical review committee(s) and approval obtained before the participation of each hospital. Similarly the study must be approved by the appropriate Competent Authority. Copies of these letters of approval are to be filed in the Sponsor trial master file and the investigator site file.

17.3 Declaration of Helsinki and ICH Good Clinical Practise
The study is to be carried out in conformation with the spirit and the letter of the declaration of Helsinki (version Tokyo 2004), and in accord with the ICH Good Clinical Practice Guidelines. The protocol, EU Clinical Trial Directive and any appropriate local laws are to be followed.

18 Data handling and record keeping

18.1 Patient Records
Each investigator is required to maintain adequate and accurate case histories designed to record all observations and data pertinent for each individual entered into the trial. Participation in the trial should be recorded in the patient notes.

Source data should include, but is not limited to:
- Date of informed consent
- Date of birth and sex
- Statement that the patient is participating in the trial
- Evaluation of eligibility criteria
- Relevant medical history and diagnosis
- Patient identifying number
- Administration of drug, including dose adjustments where required or end of trial treatments
- Study visit dates
- Physical examinations, haematological examination and bone marrow testing
- Consent for sample
- Adverse events
- Concomitant medications
- Date and reason for exclusion from treatment or trial
- Smoking history

18.2 Case Report Forms (CRF)

Data reported on the CRF, should be derived from, and consistent with, the source data. Any discrepancies should be explained. Entries on the CRF should be legible and in ink. Corrections should be made with a single line through the incorrect entry and any correction initialled and dated by the person making the correction. Correcting fluid should not be used. For the purposes of this study the CRFs should be completed in English.

Forms are sent from the CCTC annually and these should be completed and returned promptly. A copy should be retained at site in addition to that be returned to the CCTC.

CRF data and samples should be anonymised unless patient consent for full name use has been obtained.

18.3 Record Retention

The investigator at each site must make arrangements for the filing and maintenance of the essential study documents (as defined by ICH E6 Guideline for Good Clinical Practice) for duration of the trial.

The Sponsor will inform the investigator when the trial is complete and can be sent to archive. Once archived the documents should be stored for the maximum period required by applicable country regulations or the Institution procedures (which ever is the greatest).

Any change in Sponsor and consequently ownership of the data will be informed to the investigator in writing.

19 Financial and Insurance

The University of Cambridge and the Cambridge University Hospitals NHS Foundation Trust jointly sponsor this study in accordance with the UK Department of Health’s Research Governance Framework for Health and Social Care, the EU Directive on Clinical Trials (Directive 2001/20/EC) and EU Good Clinical Practice Directive (2005/28/EC). Where studies are carried out in a hospital, the hospital continues to have a duty of care to a patient being treated within that hospital, whether or not that patient is participating in a University supported study. Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.
The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

20 Publications policy

The trial steering committee is responsible for ensuring integrity of the study and approving content and distribution of all publications arising from the study. The steering committee will provide collaborators with regular information updates on the progress of the trial. Definitive publications arising from the trial will acknowledge all collaborators of the trial.

21 Supplements

Appendix I – SAE Reporting Flow Chart & SAE Form
Appendix II – Quality of Life Assessment
Appendix III – Publications
Appendix I – SAE Reporting Flow Chart

Adverse Event

Serious
(results in death; is life-threatening or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity)

Suspected Unexpected Serious Adverse Reaction
(event related to protocol drugs and not listed in protocol or summary product characteristics)

Centre to fax report to CCL immediately (defined as within 24 hours of knowledge of event) and post copy to CCTC

CCL to inform CI and Sponsor R&D Dept

Fatal or life threatening
Sponsor’s representative to report within 7 days of notification of event to CA and REC (+8 days for further information) and to send copy to all investigators concerned.

Not fatal or life threatening
Sponsor’s representative to report within 15 days of notification of event to CA and REC and to send copy to all investigators concerned.

Not Serious

Other Suspected Serious Adverse Reaction
(SSAR) or other serious adverse event not related to protocol drugs

Record in CRF and send to CCTC

Entered into database

CI to provide annual progress report to REC and copy to Sponsor.

CCL = Co-Clinical Lead (Dr CN Harrison: Fax +44 (0) 207 188 2728; call +44 (0) 207 188 2742 to confirm receipt or email: Claire.harrison@gst.nhs.uk. When Dr Harrison is out of the office, there is a clinical deputy assigned to take over her duties and information posted on the fax machine.)
PT-1 (AMENDED)
SERIOUS ADVERSE EVENT REPORT FORM –
AMENDED VERSION

ONLY COMPLETE THIS FORM IF SERIOUS ADVERSE EVENT (SAE) IS A SUSAR.
A SUSAR IS ANY SAE WHICH IS NOT EXPECTED (expected events defined in section 12 of
trial protocol) & WHICH IS JUDGED AS HAVING A REASONABLE SUSPECTED CAUSAL
RELATIONSHIP WITH A PROTOCOL DRUG.
For SSARs & other SAEs, do not complete this form but report the event on the usual annual
trial follow up forms when the forms are due.

ID: PT-1 TRIAL NUMBER: _______ PATIENT INITIALS: _____/_____/

REPORTING SITE INFORMATION
1. HOSPITAL: __________________________ 2. COUNTRY ________________
3. PRINCIPAL INVESTIGATOR _____________________________

REACTION INFORMATION
6. DATE OF BIRTH: DD/MMM/YYYY
7. SEX: [ ] M [ ] F
8. REACTION ONSET: DD/MMM/YYYY
9. CHECK ALL APPROPRIATE TO ADVERSE REACTION:
   [ ] Patient died
   [ ] Life threatening
   [ ] Involved or prolonged inpatient hospitalisation
   [ ] Persistent or significant disability/incapacity
   [ ] Congenital anomaly/birth defect
   [ ] Medically important event
10. BRIEF DESCRIPTION OF REACTION:
    __________________________________________________________________________

SUSPECT DRUG(S) INFORMATION
11. SUSPECT DRUG(S):____________________ 12. DAILY DOSE(S):
    __________________
13. ROUTE(S) OF ADMINISTRATION: __________ 14. INDICATIONS FOR USE:
    __________
15. THERAPY DATES (FROM/TO): __________ 16. THERAPY DURATION: __________
17. DID REACTION ABATE AFTER STOPPING DRUG?: [ ] YES [ ] NO [ ] N/A
18. DID REACTION REAPPEAR AFTER REINTRODUCTION?: [ ] YES [ ] NO [ ] N/A
ID: PT-1  TRIAL NUMBER: ________  PATIENT INITIALS: ____/____/____

CONCOMITANT DRUG(S) & HISTORY

19. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction):

___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________

20. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, etc.):

___________________________________________________________________________

Manufacturer Information:

OUTCOME & ADDITIONAL INFORMATION

21. OUTCOME:

☐ COMPLETELY RECOVERED - Date recovered: ____/____/____
☐ RECOVERED WITH SEQUELAE - Date recovered: ____/____/____
☐ ONGOING - at ____/____/____
☐ DIED - DATE: ____/____/____

22. ADDITIONAL INFORMATION:

___________________________________________________________________________

Name of person completing this report (please PRINT):

Date: ____/____/____ Telephone number: ___________ Signed: _______________________

Date SAE form faxed to *Clinical Co-ordinator: ____/____/____ Date posted to CCTC ____/____/____

FAX TO *CLINICAL CO-ORDINATOR ON 0207 188 2728 WITHIN 24 HOURS OF KNOWLEDGE OF EVENT. CALL 0207 188 2742 TO CONFIRM RECEIPT AND POST COPY TO:
PT1 Coordinator, Cambridge Cancer Trials Centre, Box 279 (S4), Addenbrookes Hospital, Hills Road, Cambridge, CB2 0QQ

(FOR OFFICE USE ONLY)

Clinical Co-ordinator: Date original SAE form received ____/____/____ Signed:

___________________________________________________________________________

If SUSAR: Date informed MHRA ____/____/____ Date informed lead REC ____/____/____
(If fatal/life-threatening, to report within 7 days, (+8 for further info), otherwise within 15 days)

Copy of report sent to investigator: ____/____/____ Copy of this form sent to CCTC on ____/____/____

Notify: Co-chief Investigator - Dr. Claire Harrison, St. Thomas’ Hospital, London.

SAE Form Version 5.0 June 2012
Appendix II – Quality of Life Assessment

EORTC Quality of Life Core 30 Questionnaire

Please answer all the questions by ticking the box that best applies to you. There are no right or wrong answers.

The information you provide is strictly confidential
To ensure confidentiality please do NOT write your name on this questionnaire

Current Health Condition

1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? 
   - Yes
   - No

2. Do you have any trouble taking a long walk? 
   - Not at all
   - A little
   - Quite a bit
   - Very much

3. Do you have any trouble taking a short walk outside of the house? 
   - Not at all
   - A little
   - Quite a bit
   - Very much

4. Do you have to stay in a bed or a chair for most of the day? 
   - Not at all
   - A little
   - Quite a bit
   - Very much

5. Do you need help with eating, dressing, washing yourself or using the toilet? 
   - Not at all
   - A little
   - Quite a bit
   - Very much

During the Past Week:

6. Were you limited in doing either your work or other daily activities? 
   - Not at all
   - A little
   - Quite a bit
   - Very much

7. Were you limited in pursuing your hobbies or other leisure time activities? 
   - Not at all
   - A little
   - Quite a bit
   - Very much

8. Were you short of breath? 
   - Not at all
   - A little
   - Quite a bit
   - Very much

9. Have you had pain? 
   - Not at all
   - A little
   - Quite a bit
   - Very much

10. Did you need to rest? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

11. Have you had trouble sleeping? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

12. Have you felt weak? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

13. Have you lacked appetite? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

14. Have you felt nauseated? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

15. Have you vomited? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

16. Have you been constipated? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

17. Have you had diarrhoea? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

18. Were you tired? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

19. Did pain interfere with your daily activities? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

21. Did you feel tense? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

22. Did you worry? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

23. Did you feel irritable? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

24. Did you feel depressed? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

25. Have you had difficulty remembering things? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

26. Has your physical condition or medical treatment interfered with your family life? 
    - Not at all
    - A little
    - Quite a bit
    - Very much

27. Has your physical condition or medical treatment interfered with your social activities? 
    - Not at all
    - A little
    - Quite a bit
    - Very much
28. Has your physical condition or medical treatment caused you financial difficulties? 

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?
   1 2 3 4 5 6 7 Very poor Excellent

30. How would you rate your overall quality of life during the past week?
   1 2 3 4 5 6 7 Very poor Excellent

PTO

QUALITY OF LIFE ASSESSMENT

Patients sometimes report that they have the following symptoms. This time we would like to know whether you have experienced any of these symptoms during the PAST MONTH.

DURING THE PAST MONTH, have you had problems with:

31. headache
32. palpitations
33. rapid pulse rate
34. chest pain
35. abdominal pain
36. heartburn
37. flatulence
38. weight loss
39. skin rash
40. skin itching
41. leg or foot ulcers
42. pain in fingers or toes
43. dizziness
44. blurred vision
45. numbness or tingling
46. back pain
47. sore throat
48. cough
49. ankle swelling
50. sore mouth
51. hair loss

If working, number of days off work in last month

none

If working, number of days off work in last month

none
DURING THE LAST YEAR have you had:-
1. Thrombosis (blood clot)  YES/NO
2. Heart attack  YES/NO
3. Stroke  YES/NO
4. ‘Mini-stroke’  YES/NO

Please give your date of birth: .... / .... / ....
Please give the date on which you completed this questionnaire: .... / .... / ....

THANK YOU

Please return the questionnaire in the enclosed FREEPOST envelope (no stamp required) to:

PT1 Trial Coordinator, Cambridge Cancer Trials Centre, Box 279 (S4), Addenbrookes Hospital, 
Hills Road, Cambridge, CB2 0QQ
Appendix III – Publications


