

Study Title: **Intracranial haemorrhage in thrombocytopenic
haematology patients.
A case-control study.
“InCiTe Study”**

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1. GENERAL INFORMATION

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2. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) changes	of	Details of Changes made
	1	26/02/2010			
	2	05/03/2010	Dr Lise Estcourt		Objectives clarified
	3	10/03/2010	Dr Lise Estcourt		The way in which individuals within each hospital are identified has been clarified
	4	13/04/2010	Dr Lise Estcourt		Estimated odds ratios and numbers clarified
	5	26/04/2010	Dr Lise Estcourt		Study period extended. Study management group to be set up.
	6	26/05/2010	Dr Lise Estcourt		Study changed to take account of possibility of significant under-recruitment.
	7	06/06/2010	Dr Lise Estcourt		Study changed to take account of the wide estimate in risk of ICH in study population
	8	11/06/2010	Dr Lise Estcourt		Minor grammatical changes
	9	23/07/2010	Dr Lise Estcourt		Time before first reminder to complete case report form decreased to 4 weeks Minor grammatical changes
	10	11/10/2010	Dr Lise Estcourt		Minor changes to wording
	11	08/11/2010	Dr Lise Estcourt		Minor changes to wording`

3. SYNOPSIS

Study Title	Risk Factors for intra-cranial haemorrhage in thrombocytopenic haematology patients. A case-control study.
Internal ref. no.	
Study Design	Case-control study
Study Participants	All thrombocytopenic adult haematology patients in the UK undergoing myeloablative chemotherapy or a stem cell transplant who had an intra-cranial haemorrhage within the study period (December 2010-December 2012)
Planned Sample Size	Dependent on true incidence of intracranial haemorrhage within the study population. Minimum of 78 cases and 78 controls
Follow-up duration	n/a
Planned Study Period	January 2011-December 2012
Primary Objective	What factors (e.g. age, type of haematological disease, treatment, infection) are associated with an increased risk of developing an intra-cranial haemorrhage?
Secondary Objectives	<u>Objective 1:</u> What is the incidence of intracranial haemorrhage in thrombocytopenic haematology patients? <u>Objective 2:</u> What are the short-term outcomes for these patients? (e.g. death or persistent neurological deficit)
Primary Endpoint	n/a
Secondary Endpoints	n/a
Intervention (s)	n/a

4. ABBREVIATIONS

ALL	Acute lymphocytic leukaemia
AML	Acute myeloid leukaemia
APL	Acute promyelocytic leukaemia
APTT	Activated Partial Thromboplastin Time
BCSH	British Committee for Standards in Haematology
BMT	Bone Marrow Transplant
BP	Blood pressure
BPSU	British Paediatric Surveillance Unit
BSBMT	British Society of Bone Marrow Transplant
CI	Confidence Interval
CJD	Creutzfeld-Jacob Disease
CLL	Chronic lymphocytic leukaemia
CML	Chronic myeloid leukaemia
CRP	C reactive protein
DIC	Diffuse Intravascular Coagulation
EDH	Extra-dural haemorrhage
FBC	Full blood count
FUNC Score	Predictive outcome score for patients with primary intra-cerebral haemorrhage
GvHD	Graft vs. Host Disease
HASS	Haematology Active Surveillance System
Hb	Haemoglobin
HL	Hodgkin's lymphoma
ICH	Intra-cranial haemorrhage
INR	International Normalised Ratio
IVH	Intra-ventricular haemorrhage

KG	Kilogrammes
MDS	Myelodysplastic syndrome
MDT	Multi-disciplinary team
NHL	Non-Hodgkin's lymphoma
NHSBT	NHS Blood & Transplant
OR	Odds ratio
PT	Prothrombin time
RBC	Red blood cells
RR	Relative risk
SAH	Sub-arachnoid haemorrhage
SDH	Sub-dural haemorrhage
TBI	Total body irradiation
UKOSS	United Kingdom Obstetric Surveillance System
VOD	Veno-occlusive disease

5. BACKGROUND

To advance the quality of care for haematology patients (when they are receiving intensive chemotherapy) it is important to gain a greater understanding of the risk factors for life-threatening haemorrhage. This case-control study concentrates on intra-cranial haemorrhage because it is the most serious type of bleed caused by significant thrombocytopenia. If an intra-cranial haemorrhage does not cause death it may lead to significant long-term morbidity. However, this complication of thrombocytopenia is rare, its exact incidence is uncertain and predisposing risk factors are unknown.

There have been many case reports in the literature of intra-cranial haemorrhage in patients with haematological disorders but there has been no previous attempt to prospectively study intra-cranial haemorrhage within this patient group and assess whether there are any common factors that predispose patients to this serious side-effect.

Prophylactic platelet transfusions are used to prevent patients with severe thrombocytopenia developing a life-threatening haemorrhage. The use of platelet transfusions in patients with haematological disorders accounts for a large proportion (27%) of all platelets issued in the UK (Wells *et al*, 2009). In patients with haematological malignancies, platelets issued to prevent thrombocytopenic bleeding account for over 50% of all platelets issued to that patient population (Qureshi *et al*, 2007). Platelet transfusions are not without risk and therefore a reliable marker of a patient's bleeding risk needs to be sought. A number of recently completed (Heddle *et al*, 2009; Slichter *et al*, 2010) and ongoing trials of platelet transfusion (Wandt *et al*, 2009; Stanworth *et al*, 2010) have highlighted our lack of knowledge regarding risk factors and incidence of severe and life-threatening haemorrhage.

The morning platelet count has been used, up to now, to indicate when a patient requires prophylactic platelet transfusions. The consensus from the BCSH guidelines was that patients should receive a platelet transfusion when the platelet count is $<10 \times 10^9/L$ unless there are other risk factors for haemorrhage such as sepsis, concurrent use of antibiotics or other abnormalities of haemostasis (British Committee for Standards in Haematology, 2003).

A patient's morning platelet count has not been shown to be a good predictor of haemorrhage (Friedmann *et al*, 2002). In a recent study the rate of bleeding was similar over a broad range of platelet counts ($6 - 80 \times 10^9/L$) (Slichter *et al*, 2010). Why some patients with severe thrombocytopenia bleed and others do not is unknown at the moment.

A patient's platelet count indicates only the presence of a specific number of platelets within the circulation, but does not give any information on the functional activity of these platelets, nor does it provide any information on the other factors that affect the formation of a clot.

Data on clinical factors that have been associated with an increased risk of bleeding in retrospective case series will be specifically sought within the data collection form, as well as clinical factors that have been associated with poorer platelet increments.

Basic laboratory data on the day of the haemorrhage will also be collected, as well as the platelet count in the preceding few days.

5.1 Rationale for the development of a surveillance system

Rare complications in haematological disorders are difficult to study and in consequence are often under-researched; our understanding of them is poor; and any interventions used in current clinical practice are rarely based on robust evidence. Routine sources of information are limited or unreliable

(Dixon *et al*, 1998), and comprehensive studies of uncommon haematological conditions require a large collaboration to identify relatively small numbers of patients.

BPSU

The British Paediatric Surveillance Unit (BPSU) has developed a reliable and straightforward method to study uncommon disorders of childhood and has conducted studies for almost twenty years. Since its inception more than 200 publications relating to its work have appeared in peer-reviewed journals, and a number of studies have had a significant impact on public health. BPSU surveys have been used to inform national screening committee decisions on antenatal screening. Rates of neonatal herpes and congenital toxoplasmosis were found to be too low to justify introducing a maternal screening programme. In contrast, BPSU surveillance for congenital syphilis along with other information revealed a continuing level of infection which justified the existing screening programme. A BPSU survey documented the association between Reye's syndrome and consumption of aspirin and a survey of chemistry set poisoning identified the risk of faulty packaging leading to a change of law over such packaging. The BPSU has also undertaken emergency surveillance in response to concerns about vitamin K therapy, water-births and whether variant CJD was appearing in British children (Nicoll *et al*, 2000).

UKOSS

It uses similar methodology to that developed by the BPSU to study rare disorders of pregnancy. Anonymous descriptive, case-control and cohort studies are conducted through a prospective monthly case-collection scheme. Each hospital with a consultant obstetric unit nominate four individuals (representing obstetricians, midwives, anaesthetists and perinatal risk management/ risk coordinator or equivalent) to report to UKOSS. With their paper-based monthly case-collection scheme, reporting system, and written and telephone reminder service they achieve a 92-95% response rate (personal communication Marion Knight - UKOSS).

5.2 Advantages of the surveillance system:

It can be used to describe the epidemiology of a variety of uncommon haematological disorders identified by clinicians as priority areas for research.

It allows the conduct of case-control as well as descriptive epidemiological studies.

It can make practical improvements in prevention and treatment of these uncommon conditions, and allow for more effective service planning.

5.3 Rationale for questions to be asked within the data collection form

5.3.1 Age

In the general population the risk of ICH increases with age. In a systematic review of the literature a RR of ICH 1.97 for every 10yr increase in age (95% CI 1.79 to 2.17) (Ariesen *et al*, 2003). In a pooled prospective study of over 21000 individuals there was a RR 2.06 for every 10yr increase in age (95% CI 1.76 to 2.51) (Sturgeon *et al*, 2007).

5.3.2 Sex

Some studies have shown a significantly higher rate of ICH in men. RR in general population male vs. female for ICH 3.73 (95% CI 3.28 to 4.25) (Ariesen *et al*, 2003). No difference was seen in Sturgeon *et al* (2007).

Male gender has been associated with significantly shorter platelet transfusion intervals (Slichter *et al*, 2005).

5.3.3 Ethnic Origin

Young and middle-aged blacks have a substantially higher risk of sub-arachnoid or intra-cerebral haemorrhage than whites of similar age. 2.1 x risk of SAH (95% CI 1.3 to 3.6). 1.4 x risk of intra-cerebral haemorrhage (95% CI 0.9 to 2.1) (*Broderick et al, 1992*). RR 2.56 (95% CI 1.8 to 3.65) (*Sturgeon et al, 2007*).

5.3.4 Weight

Larger patients have poorer platelet increments. An increase of 1kg in weight decreased the number of days to next transfusion by 0.01 days (*Slichter et al, 2005*). This effect was independent of gender. Whether this translates into an increased bleeding risk is unknown.

5.3.5 Smoker

Risk factor for ICH in general population. Current smoker RR 1.31 (95% CI 1.09 to 1.58) (*Ariesen et al, 2003*). No difference seen in *Sturgeon et al (2007)*.

5.3.6 Hypertension

Risk factor for ICH in general population RR 3.68 (95% CI 2.52 to 5.38) (*Ariesen et al, 2003*). Patients with systolic blood pressure (BP) \geq 160mmHg or diastolic BP \geq 110mmHg RR 5.55 (95% CI 3.07 to 10.0) (*Sturgeon et al, 2007*).

5.3.7 Diabetes

Risk factor for ICH in general population RR 1.3 (95% CI 1.02 to 1.67) (*Ariesen et al, 2003*). No difference seen in *Sturgeon et al (2007)*.

5.3.8 Site of haemorrhage

Site of haemorrhage is a predictor of functional outcome in general population (*Rost et al, 2008*).

In a recent study poor outcomes after ICH in AML patients were associated with four independent risk factors, three of which were associated with the site of the haemorrhage. Brainstem haemorrhage (P = 0.001), sub-arachnoid haemorrhage (SAH) (P = 0.017), and extra-dural haemorrhage (EDH) (P = 0.014) (*Chen et al, 2009*)

5.3.9 Volume of haemorrhage

In the general population the volume of the haematoma is one of the most important predictors of mortality and functional outcome after ICH. (*Broderick et al 1993; Hemphill et al 2001; .Rost et al 2008*).

5.3.10 Glasgow coma scale (GCS) at time of haemorrhage

In the general population this was another important predictor of functional outcome. FUNC score GCS < 9 much worse outcome (*Rost et al 2008*).

5.3.11 Clinical Factors associated with haemorrhage in haematology patients

Clinical factors that have been associated with an increased risk of bleeding in retrospective studies have included:

5.3.11.1 A recent history of severe bleeding

In a review of almost 3,000 thrombocytopenic adult patients, over a 10-year period, Friedmann

showed a significant relationship between a history of recent bleeding (within the previous five days) and occurrence of significant haemorrhage (OR 6.72; 95% CI, 5.53 to 8.18). (Friedmann *et al*, 2002)

5.3.11.2 Uraemia

In Friedmann's study, uraemia (defined as blood urea nitrogen > 50 mg/dL which equals urea > 17.9 mmol/l) was associated with an increased risk of bleeding (OR 1.64; 95% CI, 1.40 to 1.92), (Friedmann *et al*, 2002).

5.3.11.3 Recent bone marrow transplantation

In Friedmann's study a recent bone marrow transplant (under 100 days) was associated with an increased risk of bleeding (OR 1.32; 95% CI, 1.22 to 1.43) (Friedmann *et al*, 2002).

5.3.11.4 Hypoalbuminaemia

In Friedmann's study, hypoalbuminaemia (defined as a serum albumin of 2.0 gm/dL or lower) was associated with an increased risk of bleeding (OR 1.54; 95% CI, 1.33 to 1.79) (Friedmann *et al*, 2002).

5.3.11.5 Acute Graft vs. Host Disease (GvHD)

In a single centre retrospective study of 622 allogeneic transplant patients over a 20 year period 21 cases of ICH were identified. A multivariate analysis with logistic regression identified acute GVHD as the only factor that significantly influenced ICH occurrence (Najima *et al*, 2009).

In a single centre randomised controlled trial of platelet transfusions, (n = 159, of which 41 had allogeneic transplants) GvHD of any grade was associated with an increased risk of haemorrhage on univariate analysis (OR 2.8; 95% C.I. 1.2 to 8.2) (Zumberg *et al*, 2002).

5.3.11.6 Veno-occlusive disease (VOD)

Najima and Zumberg also showed a possible association of VOD of any grade with an increased risk of haemorrhage, although the confidence intervals were very wide (Hazard ratio 2.63 (95% CI 0.77 to 9.00) (Najima *et al*, 2009); (OR 4.4; 95% CI 0.6 to 27.8) (Zumberg *et al*, 2002).

5.3.11.7 Fever

In Webert's retrospective analysis (Webert *et al*, 2006) of Rebull's data (Rebulla *et al*, 1997) the presence of an elevated body temperature increased the risk of mild bleeding (grade I & II) by 52% (RR 1.52; 95% CI (1.25 to 1.85); p< 0.005) The presence of an elevated body temperature increased the risk of clinically significant bleeding (grade II - IV) by 87% (RR 1.87; 95% CI (1.40 to 2.49); p< 0.005) For clinically significant bleeding the risk of bleeding increased as the temperature increased. Risk of bleeding increased significantly when the patient's body temperature was between:

- 38-38.4 (RR 2.43; 95% CI (1.0 to 5.90); p< 0.05)
- >38.5 (RR 3.95; 95% CI (1.90 to 8.20); p=0.0001)

In a previous small study (Higby *et al*, 1974) 9 out of 13 patients who bled were febrile at the time of haemorrhage.

5.3.11.8 Use of amphotericin

Therapeutic use of amphotericin B is associated with decreased expression of glycoprotein Ib on the surface of stored platelets (Sloand *et al*, 1994). This may induce a platelet function defect. In Zumberg's study usage of amphotericin B was associated with an increased risk of bleeding (OR 3.8; 95% CI 1.3 to 10.5) (Zumberg *et al*, 2002)

5.3.11.9 Use of antibiotics

Beta lactam antibiotics have been associated with platelet dysfunction (Burroughs & Johnson 1990; Fletcher *et al*, 1986).

Cephalosporins have been associated with hypoprothrombinaemia (Sattler *et al*, 1986).

5.3.12 Clinical factors associated with an impaired platelet increment

Splenomegaly, infection and diffuse intravascular coagulation (DIC) have all been associated with poorer responses to platelet transfusion (Slichter *et al*, 2005). This may translate into an increased risk of haemorrhage.

5.3.13 Laboratory factors associated with haemorrhage

5.3.13.1 CRP

Inflammation has been shown to induce severe haemorrhage in thrombocytopenic mice (Goerge *et al*, 2008). This study will therefore collect data on CRP as well as evidence of concurrent infection at the time of haemorrhage.

5.3.13.2 Prothrombin Time

Prolonged PT was associated with a poorer outcome after ICH in AML patients ($P < 0.001$) (Chen *et al*, 2009).

5.3.13.3 Haemoglobin

A low haematocrit has been shown to be associated with an increased risk of bleeding (Valeri *et al*, 2007; Valeri *et al*, 2001; Blajchman *et al*, 1994).

5.3.13.4 Persistent Thrombocytopenia

Platelets have been shown to provide an endothelial supportive function by plugging gaps in the endothelium of otherwise intact blood vessels. Animal studies have shown that thrombocytopenia is associated with the gradual thinning of the vessel wall endothelium over time, and that, if thrombocytopenia persists, gaps gradually occur between adjacent endothelial cells (Kitchens 1975, Blajchman 1981). This thinning and fenestration of the endothelium is accompanied with on-going and increased use of circulating platelets to prevent the loss of red blood cells (RBCs) through these gaps.

In a study of 1402 bone marrow transplant (BMT) patients very low platelet counts were significantly associated with bleeding post BMT. The risk of bleeding in a patient with 3 to 7 (out of 7) days of platelet counts $<10 \times 10^9/l$ in the week preceding the haemorrhage was 40 to 60% higher than a patient with 0 to 2 days with low platelet counts. However, only 8.6% of patients who bled had such profound thrombocytopenia prior to the bleeding episode. In most cases, bleeding episodes started with platelet counts $>20 \times 10^9/l$ (Nevo *et al*, 2001).

6. OBJECTIVES

6.1 Primary Objective

What factors (e.g. age, type of haematological disease, treatment, infection) are associated with an increased risk of developing an intra-cranial haemorrhage?

6.2 Secondary Objectives

Objective 1: What is the incidence of intra-cranial haemorrhage in thrombocytopenic haematology patients?

Objective 2: What are the short-term outcomes for these patients (e.g. death within 30 days of haemorrhage, persistent neurological deficit)?

7. STUDY DESIGN

7.1 Summary of Study Design

7.2 PURPOSE AND DESIGN:

This study aims to collect anonymous data about haematological patients who have had an intracranial haemorrhage while undergoing intensive chemotherapy or a stem cell transplant. This information is key to identifying means to improve treatment and quality of care.

This information will be collected through doctors and specialist nurses in hospitals throughout the UK. An information collection system will be developed for this study and will be based on similar systems in obstetrics (UKOSS) and paediatrics (BPSU). Assistance in the development of this system will be via BSBMT and advice from UKOSS. Once this system is in place it could also be used for future studies of rare disorders and complications within haematology that are difficult to study via any other method.

The design is a case-control study.

7.3 RECRUITMENT:

Patients will be identified through a new haematological surveillance system (Haematology Active Surveillance System) "HASS", which is based on similar obstetric (UKOSS) and paediatric surveillance systems (BPSU), to study rare haematological disorders.

7.3.1.1 Case identification

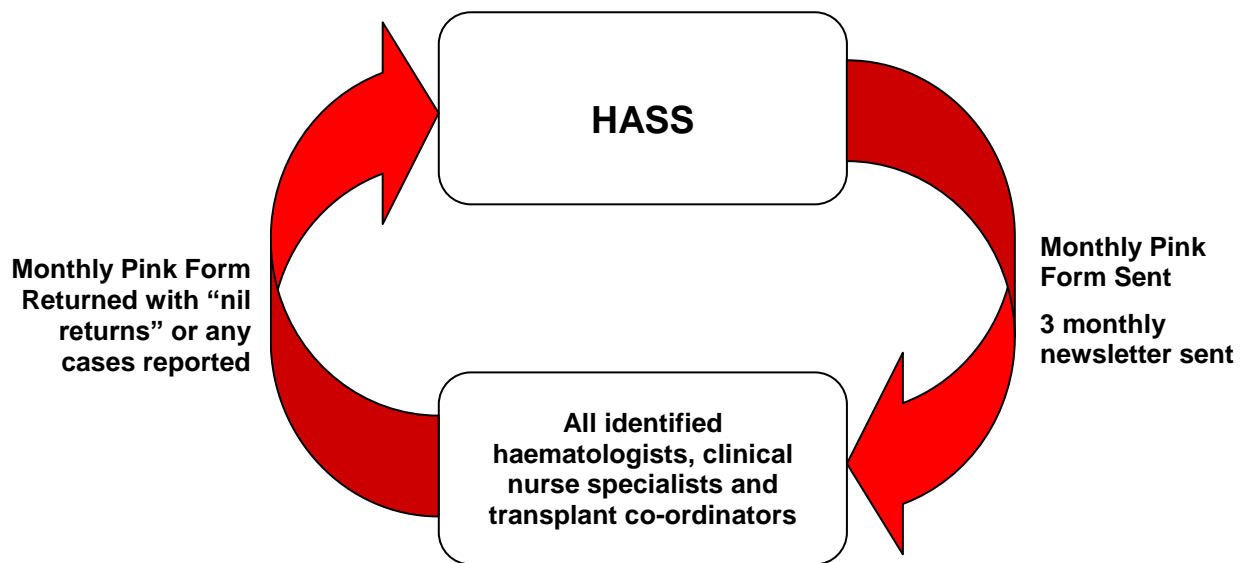
This anonymous descriptive, case-control study will be conducted through a monthly case-collection scheme. Each hospital with a haematology department caring for patients with acute leukaemia or transplant patients will identify at least four individuals (representing haematologists, specialist nurses, and transplant co-ordinators) to report to HASS.

The individuals will be identified via BSBMT (principal transplant consultant and transplant co-ordinator, specialist nurse) and individuals associated with AML-16 trial or other current leukaemia trials for non-transplant cases (principal investigator for the current leukaemia trials at each centre and research nurses associated with the trials).

Every month, the four nominated individuals will be sent a report card. They will be asked to complete a simple tick box indicating if any cases have occurred in the previous month, or if none, to return the card indicating a “nil return”.

We expect that the majority of cards each month will be “nil returns” because intra-cranial haemorrhage is a rare event. “Nil returns” are extremely important because they allow us to confirm the number of haematology patients in the denominator cohort.

On the report card, if the individuals initially identified via BSBMT and AML-16 no longer have responsibility for the transplant and non-transplant patients respectively or the individual wishes to delegate the responsibility to another individual (who is also responsible for the same patients within their trust) they can enter the correct contact details on the report card. This will mean that the following month’s report card can be sent to the appropriate person.



7.3.1.2 Control Group Identification

In order to perform the case-control study, HASS will also collect anonymised information on control patients. Clinicians who report a case will also be asked to identify an appropriate control patient and complete a similar data collection form from their case notes. If the case is a transplant patient, clinicians will be asked to identify the patient who was treated with a stem cell transplant (either allogeneic or autologous) in the same hospital immediately before the index case. If the case is a non-transplant patient, clinicians will be asked to identify the patient who was treated with intensive chemotherapy in the same hospital immediately prior to the index case.

This method has been used by UKOSS successfully in previous studies and has been shown to produce a comparison group similar in characteristics to the population as a whole.

7.4 Primary and Secondary Outcome Measures

7.5 Primary Outcome measures:

This will be an analysis of haemorrhage and associated risk factors

7.6 Secondary Outcome Measures:

The incidence of intra-cranial haemorrhage in the stem cell transplant population will be calculated with 95% confidence intervals.

The incidence of intra-cranial haemorrhage in the non-transplant patient population will only be for patients involved in the current acute leukaemia trials (to ensure accuracy of the denominator data), this will be calculated with 95% confidence intervals.

Rates of death

Rates of significant neurological deficits

7.7 Study Participants

7.8 Overall Description of Study Participants

All adult patients in the UK who have an intra-cranial haemorrhage while receiving myeloablative chemotherapy for a haematological malignancy or are receiving/about to receive a stem cell transplant.

7.9 Inclusion Criteria

- All adult haematology patients receiving myeloablative chemotherapy (defined as chemotherapy expected to cause a significant thrombocytopenia $< 50 \times 10^9/L$ for > 5 days^{*}) or a stem cell transplant that have an intra-cranial haemorrhage within the study period (1st January 2011 to 31st December 2012)
- Aged ≥ 16 yrs of age
- Only patients being treated with curative intent
- All severities of intra-cranial haemorrhage
- All types of intra-cranial haemorrhage

7.10 Exclusion Criteria

Patients are not eligible for this study if:

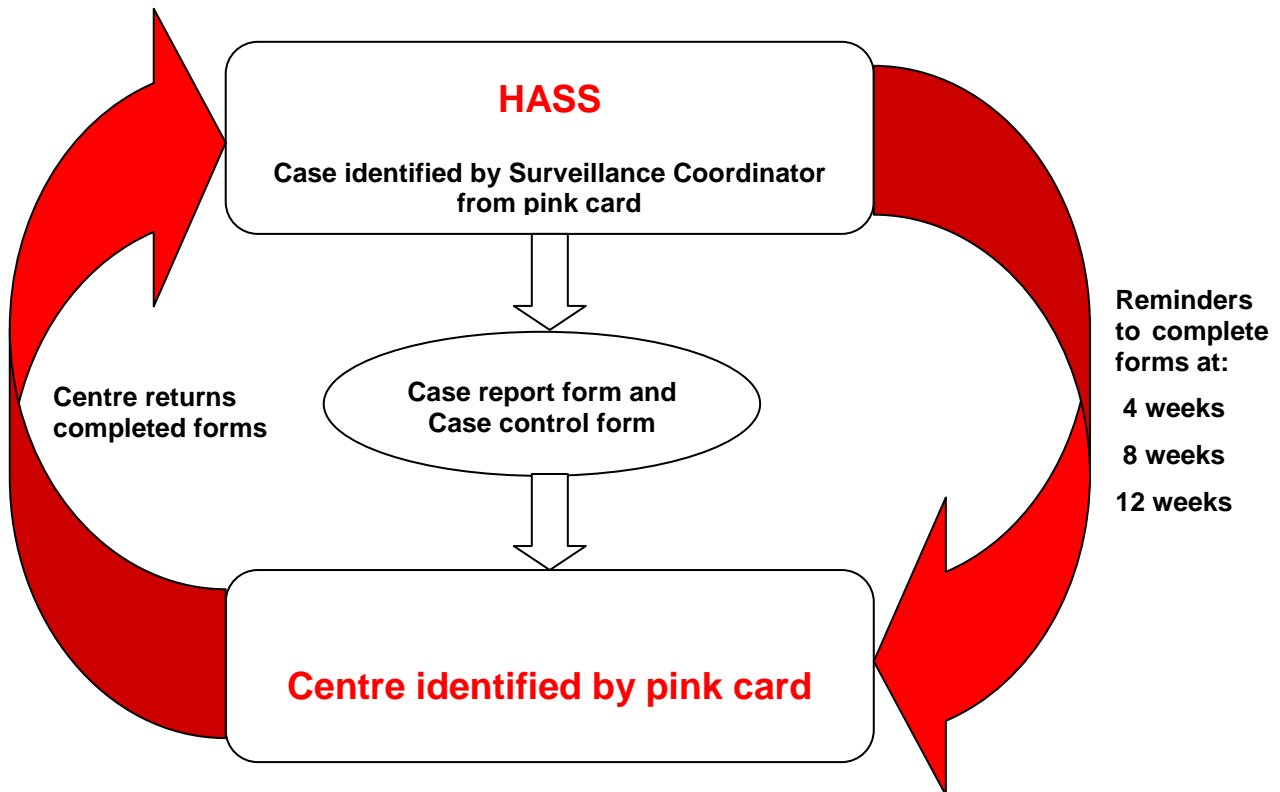
- They do not meet the inclusion criteria

7.11 Study Procedures

7.12 Data collection

On receiving a case report, the central team will dispatch a data collection form to the clinician. The data collection form will seek additional information on risk factors, management and outcomes according to the protocol. Cases will be allocated a central HASS identification number. No names, addresses, dates of birth, hospital numbers or NHS numbers will be sought. Respondents will only be asked to record the unique HASS identification number in order to facilitate elimination of duplicate reports.

* This includes AML and ALL patients; Burkitt's lymphoma patients; and relapsed lymphoma requiring e.g. DHAP/ESHAP



7.12.1.1 Facilitation of data returns

If the completed forms are not received back by the central team after four weeks, a written reminder will be sent out.

If there is still no response after a further four weeks, a further set of forms will be sent to the centre (to ensure that non-return is not due to the forms going missing) and the clinician will be contacted by telephone.

After a further four weeks the clinician will receive a further written reminder and telephone call.

All information will be anonymous and will be completed from the patient's case notes. The studies thus only involve the provision of information after the acute event has occurred. The patients' management will not be changed in any way by inclusion of their data in the study, and patients will not be contacted at any point by the central research team or by local collaborating clinicians.

7.13 Monitoring Data Collection and Returns

The response rate from reporting clinicians will be monitored throughout the course of the study, as part of the routine operation of HASS.

On the report card, if the individuals (identified via BSBMT and AML-16) no longer have responsibility for the transplant and non-transplant patients respectively they can enter the correct contact details on the report card. This will mean that the following month's report card can be sent to the appropriate person. This will improve the number of returns and avoid an inappropriate person being contacted.

A three-monthly bulletin will be produced to inform all of the reporting clinicians of response rate to the study, and number of cases reported.

7.14 Study Management Group

A study management group will be set up prior to initiation of the study to include Consultant Haematologists. This group will review the protocol prior to initiation of the study and then review data from the study at regular intervals during the study period. If the minimum number of cases have not been recruited within the two year period the study period will be extended to ensure the minimum number of cases have been recruited.

A study writing group will be formed from the study management group.

7.15 Consultation

The research design and protocol will be discussed by the Clinical Trials Committee of BSBMT. The protocol has also been reviewed externally by:

Professor David Marks Professor of Haematology and Stem Cell Transplantation,
Bristol United Healthcare Trust

7.16 Definition of End of Study

The study will be completed at the end of two years if a sufficient number of cases have been reported to allow detection of an odds ratio of 2.5 with 80% power at a 5% significance level for the risk factors of fever, amphotericin B usage and antibiotic usage.

If the study management group review does not expect the number of cases reported to reach this level of significance the duration of the study will be extended to ensure adequate numbers of cases have been recruited.

8. INTERVENTIONS

This is a surveillance study and no changes in the management of any patient will occur.

9. SAFETY REPORTING

At no point will patient care be altered, delayed or compromised for the purpose of this study. Patients will undergo their normal course of management throughout.

10. STATISTICS AND ANALYSIS PLAN

10.1 The Number of Participants

We have planned the study length to provide sufficient cases and controls to detect with 80% power at the 5% level an odds ratio of 2.5 for a range of analyses of associated factors. This will require a minimum of 78 cases (for the variables of fever, amphotericin usage and antibiotic usage); using the incidence data of these variables from previous studies (See Table 1).

Table 1: Variables and the number of cases required to detect relative risks (RR) of 1.5 to 3 with both 80% and 90% power

Variable	Estimated Incidence from studies	Number of cases required to detect with 80% power				Number of cases required to detect with 90% power			
		RR 3	RR 2.5	RR 2	RR 1.5	RR 3	RR 2.5	RR 2	RR 1.5
General factors									
Fever	0.36[†]	55	78	135	399	71	101	177	521
Amphotericin B	0.44[‡]	55	77	133	387	72	101	174	506
Uraemia	0.15[§]	77	115	212	670	100	150	277	876
Antibiotics	0.34	55	78	136	404	72	102	178	528
Transplant related Factors (estimated 50% cases will be transplant cases)									
Acute GvHD	0.25^{**}	59	86	154	470	77	112	201	613
VOD	0.14^{††}	81	120	222	705	105	157	290	920

RR = relative risk

True incidence of ICH is 0.5%	Expected number of cases within 2 years is 60
True incidence of ICH is 1%	Expected number of cases within 2 years is 120
True incidence of ICH is 1.5%	Expected number of cases within 2 years is 180
True incidence of ICH is 2%	Expected number of cases within 2 years is 240
True incidence of ICH is 2.5%	Expected number of cases within 2 years is 300

[†] Estimates for fever (0.39) Friedmann *et al* 2002 and (0.32) Slichter *et al* 2005.

[‡] Estimates for usage of Amphotericin B (0.404) Friedmann *et al* 2002 and (0.48) Slichter *et al* 2005

[§] Estimate of incidence of uraemia and usage of antibiotics Friedmann *et al* 2002

^{**} Estimate of incidence of acute GvHD (Grade III to IV) Cahn *et al* 2005

^{††} Estimate of incidence of VOD Coppell *et al* 2010

The true incidence of ICH is unknown and there are a wide range of estimates from the literature, from 0.5% to 6.9% (See Table 2). It is expected that the true estimate is between 1 to 2%, and the length of the study has used this estimate to predict the length of the study of two years.

The confidence intervals for the incidence of intra-cranial haemorrhage are broad and therefore our prediction of 120 to 240 cases reported within 2 years, although reasonable, according to the current literature, may be an over-estimate of the true figure. To take this fact into consideration, the study management review group will review the number of cases reported and ensure that the study remains open until a minimum of 78 cases and 78 controls are reported. This will allow us to detect some basic probable risk factors for haemorrhage (fever, amphotericin usage, antibiotic usage), but only if they have a very significant effect on the risk of bleeding (80% power to detect a relative risk \geq 2.5).

As the number of cases and controls increases, the study will have greater power to detect the risk factors associated with haemorrhage. It will be able to detect smaller effects (i.e. variables that produce a smaller increase in relative risk); the effects of other less common risk factors within the study population can be assessed (including factors associated with stem cell transplants such as GvHD or VOD) (See Table 1).

Table 2: Incidence of intracranial haemorrhage according to various studies

Variable	Incidence	Study Population	Study name	Number of patients in study	Total number of study days
Intracranial haemorrhage	3.4%	Allogeneic stem cell transplant patients	Najima et al 2009	622	Not reported
	6.9%	Stem cell transplant patients (90% allogeneic)	Bleggi-Torres 2002	841 patients 371 died 180 post-mortems	Not reported
	2%	Stem cell transplant patients	Nevo 1998	1402	Patients observed for 100 days post-transplant
	0.9%	Allogeneic stem cell transplant	Antonini 1998	115	Median observation 90 days post transplant
Grade 4 bleeding (this category will include ICH with neurological deficit and fatal bleeds)	0.5-1%	Mixed population	Slichter 2010	1272	24309
	2%	AML	Rebulla 1997	255	7335

One of the secondary objectives is to determine the incidence of intra-cranial haemorrhage in patients with a haematological malignancy or receiving a stem cell transplant. According to the British Society of Bone Marrow Transplant (BSBMT) registry there were 2,939 transplants performed in 2008. All stem cell transplants performed in the UK have to be reported via BSBMT to the European Group for Blood and Bone Marrow Transplantation (EBMT). We will be able to obtain accurate denominator data via BSBMT for transplant patients.

Accurate denominator data for patients with acute leukaemia will be obtained via a variety of sources Numbers recruited to AML 16 – intensive arm and AML 17 over the designated time period and ALL trials

Data from National Cancer Research Network (NCRN)

Data from Hospital Electronic Syndromic Surveillance System (HESS)

Table 3: Number of Cases of Acute Leukaemia reported in the UK in 2006

	England	Wales	Scotland	N. Ireland	UK
Cases					
Males	3,517	285	334	93	4,229
Females	2,508	193	224	83	3,008
Persons	6,025	478	558	176	7,237
Crude rate per 100,000 population					
Males	14.1	19.7	13.5	10.9	14.2
Females	9.7	12.7	8.5	9.3	9.7
Persons	11.9	16.1	10.9	10.1	11.9

If the true incidence of ICH is 0.5%, then an accurate estimate of incidence will be obtainable with 60 cases from a study population of approximately 12,000 (transplant patients (approximately 6,000 cases over 2 years) and non-transplant patients (approximately 6,000 cases over 2 years) combined). This would provide an estimate of the incidence of ICH of 0.5% with a 95% confidence interval (CI) of 0.39% to 0.64%.

Also, accurate estimates of the incidence in sub-groups could be estimated with the minimum number of cases recruited. For example, if it was assumed that there were 30 cases of ICH over two years from a population of 6,000 transplant patients, this would provide an estimate of the incidence of ICH of 0.5% (95% CI 0.35% to 0.72%).

10.2 Analysis of Endpoints

Descriptive information will be presented as frequencies or proportions with confidence intervals. Odds ratios with 95% confidence intervals will be calculated and adjusted for confounders and effect modifiers using conditional logistic regression.

Incidence rates will be calculated with 95% confidence intervals. Since all stem cell transplants within the UK have to be registered with BSBMT as a requirement of JACIE this will be used as the denominator for transplant cases.

For non-transplant cases the denominator will be the number of cases of acute leukaemia reported in the UK who have been treated intensively. Denominator data to be obtained from multiple sources including AML trials, NCRN, HESS.

11. ETHICS

This study seeks to collect information about haematological patients with an intra-cranial haemorrhage. This information is key to identifying means to improve treatment and quality of care. The collection of information about individuals in this way raises these ethical issues:

11.1 Consent

It will not be practicable to obtain consent for data collection from individual patients, as this would prevent the achievement of one of the objectives of the study, namely to document the number of patients who suffer from this complication in the UK. Accurate measurement of incidence requires documentation of ALL cases occurring in the UK.

The National Information Governance Board (formerly Patient Information Advisory Group (PIAG)) considers that organisations seeking to use patient information for research purposes without

consent should seek anonymised or pseudonymised data only and not any personally identifiable information^{‡‡}.

Accordingly, this study will not collect names, addresses, postcodes, dates of birth, hospital numbers or NHS numbers. Collection of data in this way in the absence of consent is unlikely to cause significant harm.

This study will use a methodology based on the UKOSS methodology of data collection. This UKOSS methodology has received the approval of the London Multi-Centre Research Ethics Committee (study reference 04/MRE02/45).

11.2 Participant Confidentiality

In order to maintain patient confidentiality, no identifiable information will be collected as outlined above.

11.3 Data Security

The security of all data will be maintained by storage on NHS Blood and Transplant's secure network, accessible only by the key researchers and responsible members of NHSBT who may require access to data to ensure compliance with regulations. Access by any other individuals for the purposes of any other study will only be allowed after a successful application to a Research Ethics Committee.

Dr. Lorna Williamson, Medical Director NHS Blood and Transplant will act as custodian of the data.

12. DATA HANDLING AND RECORD KEEPING

No identifiable data will be collected. All data will be coded under the unique HASS number and stored within the secure network of NHS Blood and Transplant's information technology services.

13. FINANCING AND INSURANCE

Funding from within NHSBT

14. PUBLICATION POLICY

The data from this study will be analysed and the results published as soon as possible in a scientific journal after study completion. The information will be published and distributed to all participating clinicians; it will also be available on the HASS website as well as being presented at scientific meetings.

^{‡‡} Department of Health Guidance Notes: Section 60 of the Health and Social Care Act 2001 (2002). Available at <http://www.dh.gov.uk/assetRoot/04/06/63/84/04066384.pdf>

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