In collaboration with the Children’s Cancer Leukaemia Group Supportive Care Group

Pilot of a randomised controlled trial to compare VZIG and aciclovir as post-exposure prophylaxis against chickenpox in children with cancer

PEPtalk2

Version 2.0
21st March 2013

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ISRCTN Reference Number:

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# INTRODUCTORY PAGES

<table>
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<th>Protocol Title</th>
<th>Pilot of a randomised controlled trial to compare VZIG and aciclovir as post-exposure prophylaxis against chickenpox in children with cancer</th>
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<tr>
<td>Sponsor</td>
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<td>NIHR Research for Patient Benefit</td>
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Randomisation should be performed by sites online at
https://www.cancertrials.bham.ac.uk/PEPtalk2Live
In case of any problems with online randomisation, randomisation can be performed over the phone by the CRCTU on:
☎ 0800 371 969

SAE reporting:
SAEs should be faxed to the PEPtalk2 Trials Office, CRCTU, University of Birmingham.
☎ 0121 414 9520 or 0121 414 3700

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SIGNATURE PAGE


This protocol has been approved by:

Name:                    Trial Role:          Signature:          Date:
Professor Paul Heath    Chief Investigator      21 MAR 2013

This protocol describes the PEPtalk2 trial and provides information about procedures for patients taking part in the PEPtalk2 trial. The protocol should not be used as a guide for treatment of patients not taking part in the PEPtalk2 trial.
TRIAL SYNOPSIS

**Title**
Pilot of a randomised controlled trial to compare VZIG and aciclovir as post-exposure prophylaxis against chickenpox in children with cancer.

**Short Name**
PEPtalk2.

**Trial Design**
This pilot study is a multi-centre, randomised controlled trial.

**Objectives**

**Primary objective**
The objective of this pilot trial is to establish the likely rate of patient recruitment in a projected full-scale Phase III trial and to gather data which will allow for an informed sample size calculation for the main trial.

**Secondary objectives**
- To create interest in and support for the study among paediatric oncologists
- To identify the most important costs and health-related quality of life implications and define the data to be collected for the assessment of the cost-effectiveness in a subsequent Phase III trial.
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BACKGROUND AND RATIONALE

1.1 Background

Of the 1500 children diagnosed with cancer annually in the UK and Eire, almost 25% lack immunity to varicella zoster virus (VZV), the cause of chickenpox and shingles (1). Treatment-related immunosuppression places these individuals at high risk of severe infection. To prevent death and severe morbidity, chickenpox requires the temporary suspension of chemotherapy as well as hospitalisation for intravenous antiviral treatment. Current guidelines for this group of patients emphasize the importance of minimizing their contact with VZV, and of providing post-exposure prophylaxis (PEP) should this occur. A recent survey in the UK and Eire suggested that PEP is delivered to approximately 250 children with cancer annually (1). Yet there is a striking lack of consensus on which PEP is best for this group. The gold standard has been an injection of pooled human immunoglobulin – varicella zoster immune globulin (VZIG) – that includes a high titre of antibodies to VZV, given as soon as possible after exposure. The use of VZIG is supported by solid evidence from previous studies (2-5). However, the protection obtained from VZIG is imperfect (5). VZIG is also associated with injection-associated discomfort, cost, inconvenience and possible infection risk. Aciclovir, an oral antiviral drug that is effective in the treatment of VZV and herpes simplex virus (HSV) disease, has been used as an alternative means of PEP in some UK paediatric oncology centres for over ten years. This practice is supported by an expert guideline of the Royal College of Paediatrics and Child Health (RCPCH) published in 2002, which offered VZIG and aciclovir as equivalent alternatives (6). Small observational studies in healthy children have reported varicella rates of 0-77% after PEP with aciclovir (7-9) and aciclovir was reported to prevent or ameliorate varicella in three children with acute lymphoblastic leukaemia (ALL) (10). No randomised studies have yet addressed the efficacy of aciclovir as PEP in immunocompromised patients, however, and this is an unlicensed indication for the drug. No prospective UK surveillance data have been collected to document the occurrence of varicella in relation to the mode of PEP.

Opinion is strongly polarised among UK paediatric oncologists who generally prescribe PEP on the basis of unit policy and experience and not patient preference. While this situation may be undesirable in terms of clinical governance and patient choice, it clearly demonstrates clinical equipoise and should place the UK in a unique position to perform a high quality comparative study. However, a recent survey among paediatric oncologists revealed entrenched positions on both sides of the PEP divide (1). Furthermore, there are systematic differences in practice surrounding the delivery of PEP among centres using VZIG compared with aciclovir (such as definitions of exposure and policies concerning the re-checking of serology prior to administration of PEP). These considerations suggest that only a large randomised trial could provide evidence of a quality sufficient to support a change in practice. The purpose of this pilot is to test how feasible and attractive such a trial would be to healthcare teams and patients in practice and to refine the study protocol accordingly. We also propose a formal health economic comparison of VZIG and aciclovir, with implications for a full-scale trial and resulting public health policy.

1.2 Trial Rationale

1.2.1 Justification for patient population

Primary VZV infection usually follows a benign clinical course and significant complications are uncommon in healthy children (11). By contrast, infection in immunocompromised patients can result in significant morbidity and even mortality. A feasibility study regarding PEP against VZV in children with cancer was carried out by members of the present Trial Management Group during 2010 (1). This study confirmed that VZV exposure and disease are frequent and significant clinical problems in paediatric oncology practice in the UK. The study also showed that at least a quarter of children with cancer are VZV-seronegative at diagnosis. The proportion of VZV negative children receiving cancer therapy is likely to be even higher because treatment is longer for certain malignancies that are common in younger children, e.g. ALL. Furthermore, there was a large group for whom serostatus could not be ascertained.
Despite the known risks of varicella in children with malignancy, measures to prevent this are inconsistently applied. In particular, we are aware that Department of Health advice to identify and vaccinate VZV-susceptible family members is rarely implemented.

Accurate recent figures for the incidence of varicella in children with cancer are not available, but over a period spanning the introduction of vaccination in the USA, this disease affected around 16% of children treated for ALL (12). Such patients generally require antiviral treatment in hospital as well as interruption to their own chemotherapy, and may still become very unwell. Furthermore, having acquired VZV during therapy they become susceptible to its reactivation as herpes zoster (shingles) (13,14). Varicella prevention is therefore an important goal in this patient population although there continues to be uncertainty about best practice.

1.2.2 Justification for design

The feasibility study conducted by members of the present Trial Management Group showed that varicella exposures are frequent but that the approach to PEP in paediatric cancer patients is highly polarised among centres (1). Patients are given VZIG or aciclovir in approximately equal measure. This degree of clinician bias can only be addressed by a substantial randomised controlled trial. The main objective of this pilot study is therefore to determine the likely rate of patient randomisation and to facilitate sample size calculation, in order to inform the design of a larger trial. If, for example, the pilot study is successful in recruiting 50 patients from up to seven UK centres over a 12-month period, then a larger trial that recruited from twice as many centres over a 24-month period could recruit about 200 patients. If necessary to achieve the required number of patients, recruitment could continue for longer than 24 months and/or be expanded to international centres. As many children's cancer trials are international due to the rarity of many of the tumour types, this would not require the establishment of new networks and collaborations. Hence, if the sample size calculation were to dictate a trial of up to 500 patients, the larger trial could be planned accordingly.

We plan to collect data on children who are exposed to VZV disease and on the effectiveness of PEP within this study. Previous surveys of varicella during ALL therapy have suggested a cumulative risk of varicella of around 15% (12, 15) and a 30% risk of VZV exposure (16); however, there are no recent data on VZV exposure and disease in the UK cohort. Only one descriptive study has reported successful use of aciclovir in protecting against VZV in nosocomially exposed children (17) but there are no controlled studies on aciclovir as PEP in children with cancer.

Our feasibility study highlighted an important issue of clinical governance in relation to VZV PEP in the UK. The lack of published evidence for the effectiveness of aciclovir represents a major barrier to informed decision-making. Were the two treatments equally effective, involvement of patients and families in decision-making on PEP could be promoted. Furthermore there could be a strong health economic argument for the use of antiviral therapy as opposed to VZIG. Unfortunately, in contrast to VZIG, there has been no attempt to collect prospective data on the effectiveness of aciclovir as PEP. Only a well-conducted randomised controlled trial could provide data of sufficient quality to support a change in practice. The implications of a successful pilot and later full-scale study would reach well beyond UK paediatric oncology practice.

1.2.3 Choice of treatment

Subject to VZV exposure being recognised, the long incubation period of varicella represents an opportunity for prophylactic interventions to interrupt infection and hence prevent clinical disease. The two major forms of post-exposure prophylaxis used in children with cancer are passive immunisation with VZIG and the antiviral drug aciclovir.

Solid evidence supports the protective efficacy of VZIG against severe varicella, when given early after exposure. As a result, the use of VZIG for immunocompromised patients is widely recommended (6, 18-20). However, available data suggest that varicella still occurs relatively frequently following VZIG and, although usually mild, it is occasionally severe or fatal (12, 15, 21). Furthermore, VZIG is expensive and in relatively short supply, problems that might intensify as varicella-immunised
individuals begin to enter adulthood in the USA and other countries (which are the source of the VZIG used in the UK). Additional concerns relate to the need for a painful intramuscular injection and the fact that this is a pooled blood product with attendant (theoretical) infective risk.

Aciclovir and related drugs are highly active antiviral agents, particularly against alpha herpes viruses such as VZV. Strong evidence supports their use in the immunocompromised, both as therapy for primary or secondary VZV infections and as prophylaxis against the latter following stem cell transplantation (22-24). However, very few studies document the use of aciclovir as PEP in high-risk patients. The largest experience is reported in a retrospective case series from Japan (17). This study reported very low rates of varicella after nosocomial exposure followed by aciclovir as single agent PEP (3/141) in comparison to a small number of controls who received no PEP (2/11); immunocompromised children were represented among the treatment group and cases.

Following emerging literature from Japan (where VZIG is not available) and favourable experiences of aciclovir during a hiatus in VZIG supply in the UK, guidance on PEP from the UK’s Royal College of Paediatrics and Child Health offered aciclovir as an alternative to VZIG in the immunocompromised child (6). However, these national RCPCH guidelines were published in 2002 and there is now an urgent need to provide a sound evidence base on which to update these guidelines. Two recent surveys confirm that aciclovir is the chosen form of PEP amongst paediatric oncologists at several large centres in the UK, together caring for more than 40% of the UK and Eire children’s cancer cohort (1, 25). There have been no reported cases of severe/fatal varicella following the institution of this change (11), but neither have prospective data been collected to address other aspects of aciclovir’s effectiveness as PEP.

There is no consensus on which PEP should be given to children with cancer. There are polarised opinions both at individual and unit level (1). This indicates that a formal comparison of VZIG and aciclovir is required in order to inform clinical decision-making and potentially expand patient choice or establish a new standard therapy.

Accordingly, PEPtalk2 participants who have had a significant VZV exposure will be randomised after the exposure to receive PEP in the form of either VZIG or aciclovir. VZIG will be given by intramuscular injection – dose depending on age – within 10 days of exposure. High dose oral aciclovir will commence 7 days after exposure and be given for 14 days.
2. AIMS, OBJECTIVES AND OUTCOME MEASURES

2.1 Aims and Objectives

2.1.1 Primary objective
The primary objective of this pilot trial is to establish the likely rate of patient recruitment in a projected full-scale Phase III trial and to gather data which will allow for an informed sample size calculation for the main trial.

In addition to the absolute rate of recruitment, the following parameters, relevant to the design of the main trial, will be assessed:

- the acceptability of randomisation to, and intervention with, either VZIG or aciclovir to proposed participants and their families;
- the compliance of participants with allocated therapy and with the study time-points;
- any symptomatic varicella disease occurring in trial participants within 12 (± 2) weeks of either study intervention (VZIG or aciclovir);
- varicella seroconversion rates in children who have received PEP at 12 (± 2) weeks after PEP administration.

Secondary objectives
- To create interest in and support for the study among paediatric oncologists
- To identify the most important costs and health-related quality of life implications and define the data to be collected for the assessment of the cost-effectiveness in a subsequent Phase III trial.

2.2 Outcome Measures

2.2.1 Primary outcome measure
The primary outcome measure will be the number of patients randomised within 12 months of the trial opening to recruitment. Considered in relation to the number of patients registered and the number of patients screened, this will allow an informed evaluation of the trial enrolment rate amongst eligible patients.

Data will therefore be collected on the number of patients screened for the study at each centre and the number of eligible patients at each centre who agree to registration and to randomisation. Reasons for not participating in the study will be collated, so far as reasonably possible, by means of a Screening Log (Pre-Registration) and, where relevant, a Screening Form (Pre-Randomisation). This is to help with the design of the larger trial.

In addition to the rate of enrolment, the following guidelines will also inform the design of the main study:

- compliance with allocated treatment;
- adherence to study follow up;
- acceptability of study procedures to patients and clinicians;
- proportion of scheduled quality of life surveys completed;
- proportion of patients for whom health care resource use and caregiver costs are collected.
2.2.2 Secondary outcome measures

1) Seroconversion
Seroconversion within 12 (+/- 2) weeks of administration of PEP will be assessed in this pilot study as asymptomatic seroconversion has been documented in previous uncontrolled studies. It is routine clinical practice in most hospitals to obtain a blood sample for confirmation of VZV serology prior to PEP administration. This analysis will be performed locally and will not delay the administration of PEP. An aliquot (1-2ml) from the blood sample (3-5ml) that is taken prior to PEP administration will be stored locally. A further blood sample (2-3ml) will be obtained at 12 (+/- 2) weeks after PEP and the 2 samples will be sent in batches to the national reference laboratory for analysis. It is proposed that the current national test, the Binding site assay, will be the basis for this analysis. This test has been validated by the Health Protection Agency and other investigators. The results of this assay will be analysed at the end of the study period and will be shared with local clinicians.

2) Incidence of breakthrough Varicella
Incidence of clinical varicella up to 12 (+/- 2) weeks following administration of PEP will be established. Local clinicians and the patient’s family will be expected to notify the coordinator if varicella occurs during this period. Details of any episodes of varicella will be obtained from the clinical notes, parent diary and/or at study visits and will include:

- severity scoring (Table 1). This should be completed once, ideally on Day 3 of the illness (up to Day 5).
- diagnostic confirmation by virologic examination of vesicular fluid if obtained (PCR, viral isolation)
- details of any hospital admission secondary to varicella (including intensive care)
- receipt of anti-virals other than study drug (including intravenous preparations of aciclovir)
- interruption of chemotherapy
- death

Table 1. Scale used to indicate severity of illness (reproduced by permission from A. Gershon)


<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
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<tr>
<td><strong>Rash</strong></td>
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</tr>
<tr>
<td>Number of lesions</td>
<td></td>
</tr>
<tr>
<td>1–50</td>
<td>1</td>
</tr>
<tr>
<td>51–100</td>
<td>2</td>
</tr>
<tr>
<td>101–500</td>
<td>4</td>
</tr>
<tr>
<td>&gt;500</td>
<td>6</td>
</tr>
<tr>
<td><strong>Character of lesions</strong></td>
<td></td>
</tr>
<tr>
<td>Macular or papular</td>
<td>2</td>
</tr>
<tr>
<td>Mostly vesicular</td>
<td>4</td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>4</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
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<tr>
<td>Temperature 38.8–39.9°C</td>
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<tr>
<td>Temperature, &gt;40°C</td>
<td>3</td>
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<tr>
<td><strong>Systemic signs</strong></td>
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<table>
<thead>
<tr>
<th>Pain in back or abdomen</th>
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<tr>
<td>Interstitial pneumonia</td>
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<tr>
<td>Encephalitis</td>
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<table>
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<tr>
<td>Does not appear ill</td>
<td>0</td>
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<tr>
<td>Appears moderately ill</td>
<td>2</td>
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<tr>
<td>Appears severely ill</td>
<td>5</td>
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<tr>
<td>Mild disease</td>
<td>≤7</td>
</tr>
<tr>
<td>Moderately severe disease</td>
<td>8-15</td>
</tr>
<tr>
<td>Severe disease</td>
<td>≥16</td>
</tr>
</tbody>
</table>

3) Quality of Life

Quality of Life assessment is expected to be documented by the following methods.

(A) **PEP**talk2 Treatment Diary

When PEP is initiated, the patient or his/her parent/legal representative will be encouraged to record their experiences of the randomised treatment received using the trial-specific PEP**talk**2 Treatment Diary. The Treatment Diary will be taken away by the patient or his/her parent/legal representative for completion. The expectation is that the Diary will then be brought to the follow-up appointment at 12 (+/- 2) weeks following exposure and passed to PEP**talk**2 research staff at the relevant hospital. The Treatment Diary should be reviewed and filed locally and a copy sent to CRCTU for central review.

(B) **EQ-5D**

The **EQ-5D**-3L or **EQ-5D**-Y (depending on patient age) will be administered on three occasions:

(i) when PEP is initiated;

(ii) at 2 weeks (included in the PEP**talk**2 Treatment Diary);

(iii) at the 12-week (+/- 2 weeks) follow-up appointment.

The **EQ-5D**-Y is designed for children aged 7 to 12. It can be completed by proxy (by the patient’s parent/legal representative) for children less than 7 years old.

The **EQ-5D**-3L is designed for patients aged 13+.

The relevant questionnaire should be reviewed and filed locally and a copy sent to CRCTU for central review.

(C) **PEP**talk2 Survey

At the 12-week (+/- 2 weeks) follow-up appointment, the patient and their family will be invited to participate in a survey to discuss their experiences further.

4) Clinician Survey

After randomisation, the clinicians caring for the children recruited to the study will be asked to complete a brief survey of their views on the randomisation process and the trial in general.
5) Evaluation of economic endpoints and preliminary cost-effectiveness
The economic outcome measure will be the incremental cost per quality-adjusted life year (QALY) gained of VZIG compared to aciclovir. In order to estimate this, the following economic endpoints will be collected during the study.

- Health-related quality of life in children in both arms, using the EQ-5D administered to patients and their caregivers;
- Staff costs of obtaining and administering the intervention;
- Indirect costs to patients' caregivers (such as travel expenses and time lost to seek healthcare).

These data will be used in a preliminary cost-effectiveness analysis of each intervention. The sample size is too small for the economic outcome estimates (incremental cost per QALY gained) to be robust enough to inform medical decision-making. However, we will use them to inform the design of a full economic analysis in a Phase III trial by:

i. Conducting sensitivity analyses to investigate the importance of each source of cost and utility information on the conclusions of the analysis

ii. Estimating the expected value of perfect information (EVPI) and expected value of partial information (EVPPI) for key parameters to determine the most cost-effective direction to conduct further studies

iii. Cross-validating the results of EQ-5D with clinical severity scores and health care use to determine whether the questionnaire is suitable for the Phase III trial

iv. Investigating whether administering the EQ-5D at 0, 2 and 12 (+/- 2) weeks is sufficient to detect differences in quality adjusted life years (QALY) between the two interventions. QALY differences will be estimated using the area under the triangle constructed by linearly interpolating between EQ-5D scores at the 3 data collection times.

Economic evaluation will be conducted according to the reference case used by the National Institute for Health and Clinical Excellence (NICE), which have also been adopted by the Joint Committee on Vaccination and Immunisation (JCVI). This will include taking a health care provider perspective, discounting costs and outcomes at 3.5% per annum and using a time horizon that captures all relevant costs and benefits.
3. TRIAL DESIGN

This pilot study is a multi-centre, randomised controlled trial. It is an exploratory trial intended to prepare for a full-scale Phase III trial comparing VZIG with aciclovir as options for post-exposure prophylaxis in children with cancer. It is planned to recruit 50 children from selected centres over a 12-month period.

VZV-seronegative children will be randomised to receive either VZIG or aciclovir following significant exposure to varicella. Blood for VZV serology will be taken at the time of exposure and at 12 weeks (+/- 2 weeks) following exposure. For all participants, information on healthcare usage will be collected. For participants who develop chickenpox, information on disease severity will also be collected. Patients and their families will be given a PEPtalk2 Treatment Diary (including both trial-specific questions and a standardised EQ-5D questionnaire) to record their experiences and to collect information about the impact on quality of life. They will also receive an EQ-5D questionnaire to complete at a follow-up appointment 12 (+/- 2) weeks after exposure. Information will be collected about the cost of each intervention (both drug costs and staff time for administration).

Deviations from timings will not necessarily be considered a deviation from protocol but must be reported.

Children who develop VZV despite prophylaxis should be treated according to standard supportive care protocols.
Figure 1. Overview of trial design

- Expected to receive, receiving, or within 3 months of having received, immunocompromising treatment for diagnosed cancer
- VZV seronegative, EITHER tested per standard paediatric practice upon cancer diagnosis OR tested after consent for trial registration, by additional test for VZV serostatus
- Consent for registration
- All eligibility criteria satisfied

REGISTRATION
PEPtalk2 Card given

VZV EXPOSURE

- Contact clinician and trial coordinator
- Test for VZV serology EITHER tested per standard practice for paediatric cancer patients upon VZV exposure OR tested after consent for trial randomisation as a trial-specific test
- PEPtalk2 Treatment Diary given after consent

RANDOMISATION

One dose of VZIG (intra-muscular)
Dose according to age*

Oral aciclovir (14 days)
Dose according to age*

CONTACT BY TELEPHONE OR EMAIL 2 WEEKS FROM EXPOSURE

FOLLOW-UP APPOINTMENT 12 WEEKS (+/- 2) FROM EXPOSURE
- Test for VZV seroconversion
- EQ-5D and PEPtalk2 Survey

Patients without VZV exposure while immunocompromised do not proceed to randomisation or follow-up.

* Dose varies according to age, per RCPCH guidelines: see section 8.2 below.
4. ELIGIBILITY

4.1 Trial Inclusion Criteria – Registration
a) Under 16 years of age.
b) EITHER diagnosed with cancer such that there is a standard expectation of immunocompromising therapy
   OR currently receiving immunocompromising treatment for cancer
   OR within 3 months of having received immunocompromising treatment for cancer.
c) No current or previous allogeneic or autologous haemopoietic stem cell transplantation / rescue.
d) Negative VZV serostatus result at cancer diagnosis or negative VZV serostatus result within the last 3 months as assessed locally.
e) Written informed consent to registration received from parent/legal representative and, where appropriate, written patient assent.

Note: refer to section 5.1.1 for further information.

4.2 Trial Exclusion Criteria – Registration
a) 16 years of age or over.
b) Current or previous allogeneic or autologous haemopoietic stem cell transplant/rescue.
c) Positive VZV serostatus result as assessed locally within the last 3 months.

Note: renal impairment and thrombocytopenia are not absolute contraindications for registration as they might resolve by the time a chickenpox exposure and screening for randomisation occur.

4.3 Trial Inclusion Criteria – Randomisation
a) Patient has previously been registered in the PEPtalk2 trial, having satisfied all registration requirements.
b) Registration criterion (c) continues to apply.
c) Immunocompromising treatment for cancer must have been initiated prior to VZV exposure.
d) Patient is able to commence either VZIG no more than 10 days after experiencing VZV exposure, or aciclovir at 7 days after experiencing VZV exposure (see sections 5.1.2 and 5.1.3).
e) No renal impairment. Renal impairment is expressed in terms of glomerular filtration rate (ml/min/1.73m²).
   Child over 1 year: Estimated glomerular filtration rate (ml/min/1.73m2) = 40 x height (cm) x serum creatinine (micromol/litre).
   Normal renal function: > or equal to 90ml/min/1.73m².
f) Written informed consent to randomisation received from parent/legal representative and, where appropriate, written patient assent.

Important note regarding thrombocytopenia: platelets must be > 50 x 10⁹/L to receive an intramuscular injection of VZIG. Therefore, if a child is randomised to receive VZIG and platelets are found to be < 50 x 10⁹/L no more than 48 hours prior to VZIG administration, arrangements must be made by local staff to administer a platelet transfusion prior to VZIG injection. There are no criteria for platelet count if randomised to aciclovir.

4.4 Trial Exclusion Criteria - Randomisation
a) Positive VZV serostatus result at time of screening.
b) Contraindication to either aciclovir or VZIG, including –
   (i) thrombocytopenia (platelets < 50 x 10⁹/L) that has not been corrected by platelet transfusion;
   (ii) renal impairment (exclude any child with GFR below 90ml/min/1.73m2);
   (iii) any other contraindications deemed to be relevant by the local Investigator or the Sponsor’s Clinical Coordinator(s).
c) Inability to start either VZIG within 10 days of VZV exposure, or aciclovir at 7 days after VZV exposure.
d) More than one VZV exposure within the past 12 weeks.

e) Inability to tolerate medications via oral or enteral route.

f) Pregnancy or lactation.
5. SCREENING AND CONSENT

5.1 Screening

5.1.1 Screening prior to registration

All patients must have a blood test confirming VZV seronegativity either at cancer diagnosis or within 3 months prior to registration. This can be a non-trial-specific test IF it occurs per standard paediatric practice following cancer diagnosis.

Patients who have a previous VZV serostatus result (whether positive or negative) taken greater than 3 months prior to trial registration may be eligible to be registered if a repeat VZV serostatus is taken and shows negative VZV serostatus. (All other eligibility criteria must also be satisfied for registration to proceed.) However, this repeat test is trial-specific and written informed consent to trial registration must be obtained beforehand.

Patients who have no prior recorded result for VZV serostatus can be tested for VZV serostatus prior to potential registration. This test is trial-specific and written informed consent to trial registration must be obtained beforehand. If the test shows VZV seronegativity and all other eligibility criteria are satisfied, the child can be registered.

5.1.2 Timing of exposure in relation to onset of rash in the index case

PEP should be restricted to patients exposed to a case of chickenpox between 48 hours before onset of rash until crusting of lesions (chickenpox).

5.1.3 Closeness and duration of contact

Prospective participants will be screened to ensure that PEP is administered only to those who have had close contact with chickenpox, including any of the following criteria:

- any household exposure
- non-household exposure by means of:
  - contact in the same room, e.g. in a classroom or a two-to four-bed hospital bay, for 15 minutes or more
  - face-to-face contact, e.g. while having a conversation.

5.1.4 Screening prior to randomisation

Following exposure to chickenpox, all patients must have a blood test re-confirming VZV seronegativity prior to randomisation. This can be a non-trial-specific test IF it occurs per standard practice for paediatric cancer patients following VZV exposure. In hospitals where this is not a routine test, the test is trial-specific and written informed consent to randomisation must be obtained beforehand.

5.2 Informed Consent

As PEPtalk2 has a two-stage enrolment process, beginning with registration and then (in the event of a chickenpox exposure) followed by randomisation, written informed consent from the patient’s legal representative – and, if appropriate, assent from the patient – must be obtained at both stages.

It is the responsibility of the Investigator to obtain written informed consent from the patient’s legal representative – and, if appropriate, to obtain assent from the patient – prior to performing any trial related procedure. (This duty can be delegated to a co-investigator, subject to such delegation of duty being recorded on the Site Signature and Delegation Log.) Patient Information Sheets and Parent/Guardian Information Sheets are provided to facilitate this process. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the patient’s legal representative and, if appropriate, to the patient. The Investigator should also stress that both the patient and their legal representative are completely free to refuse participation in, or to withdraw from, the trial at any time. The patient’s legal representative –
and, if appropriate, the patient – should be given ample time to read the relevant Information Sheet(s) and to discuss participation with others outside the site research team.

The patient and their legal representative must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient and their legal representative to refuse participation in the trial, without giving a reason, must be respected.

If the patient's legal representative expresses an interest in the patient participating in the trial, and the patient does not expressly refuse, the patient’s legal representative should be asked to sign and date the latest version of the Informed Consent Form. In addition, if possible and within reason, the patient should be asked to sign the Assent Form. If it is not reasonably practical to secure the patient’s assent, the Investigator must provide an explanation on the Assent Form.

The Investigator must then sign and date both the Informed Consent Form and the Assent Form. A copy of both forms should be given to the patient’s legal representative; a copy of both should be filed in the hospital notes; and the originals should be placed in the Investigator Site File (ISF). Once the patient is entered into the trial, the patient’s trial number should be entered on the Informed Consent Form and Assent Form maintained in the ISF. In addition, a copy of the signed Informed Consent Form and a copy of the Assent Form must be sent in the post to the Trials Office for review.

Details of the informed consent discussions should be recorded in the patient’s medical notes. This should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the Patient Information Sheet, Informed Consent Form and Assent Form. Throughout the trial the patient and their legal representative should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient’s continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient’s legal representative and attempt to re-assent the patient, in which case the process above should be followed and the right of both the patient and their legal representative to withdraw the patient from the trial respected.

Electronic copies of the Patient Information Sheets, Parent/Guardian Information Sheet, Informed Consent Form and Assent Form are available from the Trials Office and should be printed or photocopied onto the headed paper of the local institution.

Details of all patients approached about the trial should be recorded on the Patient Screening and Enrolment Log. Details of all patients registered in PEPtralk2 should be recorded on the Patient ID Log. With the prior consent of the patient’s legal representative, the patient’s General Practitioner (GP) should also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose.
6. **TRIAL ENTRY**

6.1 **Registration**

All prospective PEPtalk2 patients must have been diagnosed with cancer such that there is a standard expectation of immunocompromising therapy. The pre-consent consultation with each prospective trial patient’s legal representative – and, if practical, with the patient – should occur as soon as possible after this diagnosis. It is standard practice to ascertain the clinical history of past infection and the current VZV serostatus of all new patients with a diagnosis of cancer being treated at a paediatric oncology principal treatment centre. This is done prior to commencement of chemotherapy and prior to administration of blood products (6). Therefore, a good opportunity for a preliminary discussion about PEPtalk2 is when VZV serostatus results from the standard test are made available to the patient’s legal representative, with counselling regarding VZV exposure and advice.

Alternatively, patients whose VZV serostatus has been checked more than 3 months ago, or for whom the standard test was missed, are also potentially eligible for enrolment. In such cases, however, the patient’s VZV serostatus will need to be (re-)tested at a non-standard time-point. This test will therefore be a non-standard, trial-specific test. Accordingly, such patients’ legal representatives will need to give written informed consent for the patient’s trial entry **prior** to the patient being tested for VZV serostatus.

Following the pre-consent consultation, written informed consent by the patient’s legal representative, patient assent (where appropriate) and confirmation of eligibility by an authorised Investigator, the patient can be registered.

When the patient is registered, their legal representative will be provided with a PEPtalk2 Card, containing details of whom to contact should an exposure to VZV occur.

6.2 **Randomisation**

In the event of an exposure as detailed in section 5.1, a registered PEPtalk2 patient becomes potentially eligible for randomisation to either VZIG or aciclovir.

Following a new pre-consent consultation, written informed consent to randomisation by the patient’s legal representative, patient assent (where appropriate) to randomisation and confirmation of eligibility by an authorised Investigator, the patient can be randomised.

Assessment of eligibility will include a new test for VZV serostatus. This can be a non-trial-specific test **IF** it occurs per standard practice for paediatric cancer patients following VZV exposure. In hospitals where this is not a routine test, the test is trial-specific and written informed consent to randomisation must be obtained beforehand.

Following confirmation of eligibility by an authorised investigator, the patient can be randomised.

Randomisation must occur as soon as possible and within 7 days of exposure to VZV. This is because one of the two forms of PEP to which patients may be allocated randomly (aciclovir) **must** be administered on Day 7 following exposure.

6.3 **Re-Exposure**

If, after randomisation to PEP and commencement of treatment, a study participant has a further exposure to VZV during the study period, the following applies:

a. If originally randomised to **VZIG** and re-exposure occurs **within** 3 weeks of receiving VZIG, no further PEP is required (either VZIG or aciclovir);

b. If originally randomised to **VZIG** and re-exposure occurs **after** 3 weeks of receiving VZIG, the local clinician, with input from family, should choose whether the patient should receive VZIG again or aciclovir. The Treatment Diary should be re-issued and data collated regarding second exposure and any subsequent varicella;

c. If originally randomised to **aciclovir** and re-exposure occurs **within** 3 weeks of receiving aciclovir, the local clinician, with input from family, should choose whether study participant
should receive aciclovir again or VZIG. The Treatment Diary should be re-issued and data collated regarding second exposure and any subsequent varicella;

d. If originally randomised to aciclovir and re-exposure occurs after 3 weeks of receiving aciclovir, local clinician with input from family to choose whether study participant should receive aciclovir again or VZIG. The Treatment Diary should be re-issued and data collated regarding second exposure and any subsequent varicella.
7. ASSESSMENTS & SAMPLE COLLECTION

7.1 Assessments

7.1.1 Blood chemistry
A blood test for routine blood chemistry (must include creatinine) will be taken prior to PEP administration. This will be tested locally. Estimated glomerular filtration rate (GFR) (ml/min/1.73m$^2$) will be calculated using the formula GFR = 40 x height (cm) x serum creatinine (micromol/litre). Any child with estimated GFR below 90ml/min/1.73m$^2$ will not be eligible for randomisation.

7.1.2 Haematology
A blood test for routine haematology (which must include platelet count) will be taken no more than 48 hours prior to VZIG administration prior to PEP administration. This will be tested locally. Any child with platelet count of below 50 x 10$^9$/L will need to receive platelet transfusion if randomised to receive VZIG intramuscular injection.

7.1.3 Physical examination/symptom assessment
All study participants will be seen by a doctor following exposure. A symptom assessment and physical examination, including height and weight measurements, will be done at this time.

7.2 Sample Collection

Blood samples
It is routine clinical practice to obtain a blood sample for confirmation of VZV serology prior to PEP administration. This analysis will be performed locally and will not delay the administration of PEP. (In hospitals where this is not a routine test, the test is trial-specific and written informed consent to randomisation must be obtained beforehand.)

An aliquot (1-2ml) from the blood sample (3-5ml) that is taken prior to PEP administration will be stored locally. Furthermore, blood will be taken for haematology and routine biochemistry (as in section 7.3). These tests will be analysed locally.

A further blood sample (2-3ml) will be obtained at 12 weeks (+/- 2 weeks) after PEP and the 2 samples will be sent in batches to the national reference laboratory for analysis at the following address:

PEPtalk2 Samples
C/o Dr Kevin Brown
Virus Reference Department
HPA Microbiology Services
Health Protection Agency
61 Colindale Avenue
London, NW9 5EQ

It is proposed that the current national test, the Binding site assay, will be the basis for this analysis. This test has been validated by the Health Protection Agency. The results of this assay will be analysed at the end of the study period and will be shared with local clinicians.

The two samples that will be tested at the national reference laboratory will be taken prior to PEP administration and at 12 weeks (+/- 2 weeks) after PEP. These serum samples should be kept frozen at -20°C or below until testing. If samples are batched and frozen locally, they must be sent frozen. It is imperative to avoid multiple freeze thaw cycles.
8. TREATMENT DETAILS

8.1 Investigational Medicinal Products
Both VZIG and aciclovir are Investigational Medicinal Products in the context of this trial.

8.2 Trial Treatment
Study participants who have had a significant VZV exposure (as defined in section 5.1) will be randomised to receive PEP in the form of VZIG or aciclovir after the exposure. VZIG intramuscular injection must be administered at the patient’s randomising hospital. Aciclovir must be dispensed by pharmacy at the patient’s randomising hospital.

8.2.1. VZIG (19)
Two licensed VZIG preparations are available in the UK: VZIG distributed in England and Wales is made by the Bio Products Laboratory (BPL), Elstree.

VZIG is prepared from pooled plasma of non-UK donors with suitably high titres of VZV antibody. The supply of VZIG is limited by the availability of suitable donors and its use is restricted to those at greatest risk and for whom there is evidence that it is likely to be effective.

Because of a theoretical risk of transmission of vCJD from plasma products, VZIG used in the UK is now prepared from plasma sourced from outside the UK, and supplies are scarce. All donors are screened for HIV, hepatitis B and C, and all plasma pools are tested for the presence of RNA from these viruses. A solvent detergent inactivation step for envelope viruses is included in the production process.

VZIG should be stored in a refrigerator between +2°C and +8°C. These products are tolerant to ambient temperatures for up to one week. They can be distributed in sturdy packaging outside the cold chain if needed.

See further the Reference Safety Information provided for the PEPtalk2 trial.

8.2.2. Aciclovir
Aciclovir is a synthetic nucleoside analogue active against herpesviruses. It should be stored between 15° to 25°C (59° to 77°F).

See further the Reference Safety Information provided for the PEPtalk2 trial.

8.3 Treatment Schedule

8.3.1 VZIG
VZIG will be given by intramuscular injection – dose depending on age – as soon as possible and within 10 days of exposure.

The dosage for the BPL product is:

- 0–5 years, 250mg (one vial)
- 6–10 years, 500mg (two vials)
- 11–14 years, 750mg (three vials)
- 15 years or over, 1000mg (four vials).

VZIG should be given intramuscularly in either the anterolateral aspect of thigh or the deltoid.

All patients will be observed for 30 minutes following administration of either VZIG with appropriate medical treatment and supervision readily available in case of a rare anaphylactic event. The date of administration, batch number and expiry date and site of administration will be recorded in the patients’ hospital records as well as documented on the CRF.
8.3.2 Aciclovir
High dose oral aciclovir will be given for 14 days, from Day 7 to Day 21 following exposure.

Aciclovir dose is per BNF for Children:

- Under 2 years age 200 mg four times daily
- 2-6 years age 400 mg four times daily
- Over 6 years age 800 mg four times daily

The date of administration, batch number and expiry date and type of preparation will be recorded in the patients’ hospital records as well as documented on the CRF.

8.4 Treatment Compliance
Treatment compliance among randomised patients will be monitored by means of the PEPtalk2 Treatment Diary and by counting tablets / measuring volume of liquid returned at follow-up visit 12 weeks (+/- 2 weeks) following chickenpox exposure.

8.5 Supportive Treatment
Study participants will be asked to report any evidence of clinical varicella following the administration of PEP to their clinician immediately. Appropriate action will be taken by the clinical team who will in turn report it to the trial office.

8.6 Concomitant Medication

8.6.1 Permitted medications
Current practice does not stipulate that chemotherapy and other medications should be stopped while PEP is administered. Therefore, all current medications are permitted.

8.6.2 Excluded medications
VZIG may interfere with immune response to live vaccines but study participants should not be receiving live vaccines during cancer treatment.
9. PATIENT FOLLOW-UP & WITHDRAWAL

9.1 Patient Follow Up

It is expected that study participants will be followed up for 12 (+/- 2) weeks following PEP administration. Once the PEP has been initiated, parents will be encouraged to record their experiences of the treatment their child receives using a Treatment Diary. This will be semi-structured with some questions and areas for free text. It will also include the EQ-5D-Y for assessment of quality of life at the time of PEP administration. The diary will be taken home by the families and they will be prompted to complete further study specific questions and another EQ-5D-Y at two and twelve weeks after PEP administration. A parent/proxy version of EQ-5D-Y for younger children will be available. At the 12 (+/- 2) week follow-up appointment, the patient and their family will be invited to participate in a semi-structured survey to discuss their experiences of the trial further. A second 3-5ml blood sample will be obtained at 12 (+/- 2) weeks after PEP.

9.2 Patient Withdrawal

9.2.1 Withdrawal from PEPtalk2 trial treatment

If a patient stops PEPtalk2 protocol treatment, the reason should be recorded in the patient’s medical notes. It should be reported to the Trial Office whether it is due to either the patient’s, parent’s or clinician’s decision. Reasons for withdrawal from protocol treatment may include, but are not limited to:

- The patient withdraws consent to further trial treatment
- Unacceptable toxicity
- Disease progression whilst on therapy

PEPtalk2 will be analysed on an “intention-to-treat” basis and any patients withdrawn from trial treatment will remain in the trial for follow-up unless the patient/parent explicitly withdraws consent for data collection (see section 9.2.2).

9.2.2 Withdrawal of consent to data collection

A patient/parent’s wishes with respect to their data must be respected. If a patient/parent explicitly states that they do not wish for any further data to be collected, this must be recorded on the relevant CRF. Details should also be recorded in the patient’s hospital records and no further CRFs must be completed.

9.2.3 Loss to follow-up

If a patient is lost to follow-up, every effort should be made to contact the patient’s General Practitioner (if consent has been obtained to notify GP of patient’s inclusion) to obtain information on the patient’s status. Similarly, if a patient’s care is transferred to another clinician, the PEPtalk2 Trial Office should be informed.
10. ADVERSE EVENT REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Definitions of different types of AE are listed in Appendix 3. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the Summary of Product Characteristics.

10.1 Reporting Requirements

Reporting requirements for the PEPtalk2 trial commence at the time of randomisation. They do not apply to patients who have been registered but not yet randomised, as there is no trial-related treatment prior to randomisation.

10.1.1 Adverse Events

As the safety profiles of the Investigational Medicinal Products used in this trial are well characterised, Adverse Reactions (ARs) experienced during treatment will be reported via the PEPtalk2 Treatment Diary.

10.1.2 Serious Adverse Events

Investigators should report all AEs that meet the definition of an SAE (see Appendix 3 for definition).

10.1.3 Monitoring pregnancies for potential Serious Adverse Events

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects.

In the event that a patient or their partner becomes pregnant during the SAE reporting period please complete a Pregnancy Notification Form (providing the patient's details) and return to the Trials Office as soon as possible. The patient should be given a Pregnancy Release of Information Form or the patient should be asked to give this to their partner. If the patient/partner is happy to provide information on the outcome of their pregnancy they should sign the Pregnancy Release of Information Form. Once consent has been obtained, provide details of the outcome of the pregnancy on a follow-up Pregnancy Notification Form and if necessary also complete an SAE Form.

10.1.4 Reporting period

Details of all SAEs will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment.

10.1.5 Post-study SARs and SUSARs

SAEs that are judged to be at least possibly related to the IMPs must still be reported in an expedited manner irrespective of how long after IMP administration the reaction occurred.

10.2 Reporting Procedure

10.2.1 Site

10.2.1.1 Adverse Events

AEs experienced during treatment should be recorded in the toxicity section of the Treatment Form. AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (see Appendix 4). Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

10.2.1.2 Serious Adverse Events

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in section 5 of the Investigator Site File (ISF).

PEPtalk2 Protocol, University of Birmingham, Cancer Research UK Clinical Trials Unit, Version 2.0, 21-Mar-2013
AEs defined as serious and which require reporting as an SAE (excluding events listed in Section 8.1 above) should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.0.

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed together with a SAE Fax Cover Sheet to the Trials Office using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the SAE Form with an SAE Fax Cover Sheet to:

0121 414 9520 or 0121 414 3700

On receipt the Trials Office will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the Trials Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the Trials Office should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the Trials Office in the post and a copy kept in the ISF.

Investigators should also report SAEs to their own Trust in accordance with local practice.

10.2.1.3 Provision of follow-up information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

10.2.2 Trials Office

On receipt of an SAE Form, seriousness and causality will be determined independently by a Clinical Coordinator, who will be either the Chief Investigator or a designated deputy. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the Summary of Product Characteristics) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

10.2.3 Reporting to the Competent Authority and main Research Ethics Committee

10.2.3.1 Suspected Unexpected Serious Adverse Reactions

The Trials Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) and main Research Ethics Committee (REC) within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days.

10.2.3.2 Serious Adverse Reactions

The Trials Office will report details of all SARs (including SUSARs) to the MHRA and main REC annually from the date of the Clinical Trial Authorisation, in the form of an Annual Safety Report.

10.2.3.3 Adverse Events

Details of all AEs will be reported to the MHRA on request.
10.2.3.4 Other safety issues identified during the course of the trial
The MHRA and main REC will be notified immediately if a significant safety issue is identified during the course of the trial.

10.2.4 Investigators
Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

10.2.5 Data Monitoring Committee
The independent Data Monitoring Committee (DMC) will review all SAEs.
### 11. DATA HANDLING AND RECORD KEEPING

#### 11.1 Data Collection

The Case Report Form (CRF) will comprise the following forms:

<table>
<thead>
<tr>
<th>Form</th>
<th>Summary of data recorded</th>
<th>Schedule for submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening Log (Pre-Registration)</td>
<td>Screening date; whether or not registered; if applicable and available, reason for not registering</td>
<td>3-monthly</td>
</tr>
<tr>
<td>Informed Consent (Registration)</td>
<td>Consent by parent or legal representative to child's registration</td>
<td>As soon as possible after registration</td>
</tr>
<tr>
<td>Child Assent (Registration)</td>
<td>Assent by child to registration OR explanatory note by clinician if assent unobtainable</td>
<td>As soon as possible after registration</td>
</tr>
<tr>
<td>Eligibility Checklist (Registration)</td>
<td>Confirmation of eligibility</td>
<td>Faxed at point of registration</td>
</tr>
<tr>
<td>Registration Form</td>
<td>Patient details</td>
<td>As soon as possible after registration</td>
</tr>
<tr>
<td>Informed Consent (Randomisation)</td>
<td>Consent by parent or legal representative to child’s randomisation</td>
<td>As soon as possible after randomisation</td>
</tr>
<tr>
<td>Child Assent (Randomisation)</td>
<td>Assent by child to randomisation OR explanatory note by clinician if assent unobtainable</td>
<td>As soon as possible after randomisation</td>
</tr>
<tr>
<td>Eligibility Checklist (Randomisation)</td>
<td>Confirmation of eligibility</td>
<td>Faxed at point of randomisation</td>
</tr>
<tr>
<td>Screening Form (Pre-Randomisation)</td>
<td>Details of exposure to varicella</td>
<td>Faxed at point of randomisation</td>
</tr>
<tr>
<td>Randomisation Form</td>
<td>Patient details; optional consent issues</td>
<td>As soon as possible after randomisation</td>
</tr>
<tr>
<td>Treatment Form</td>
<td>Details of treatment</td>
<td>Within 1 month of treatment</td>
</tr>
<tr>
<td>PEPtalk2 Treatment Diary</td>
<td>Quality of Life and Adverse Event data</td>
<td>Within 1 month of treatment</td>
</tr>
<tr>
<td>PEPtalk2 Patient Survey</td>
<td>Feedback from parents/patients about their views on trial processes and documentation</td>
<td>Within 1 month of treatment</td>
</tr>
<tr>
<td>PEPtalk2 Clinician Survey</td>
<td>Feedback from clinicians about their views on trial processes and documentation</td>
<td>Within 1 month of treatment</td>
</tr>
<tr>
<td>Follow-Up Form</td>
<td>Details of follow-up appointment at 12 weeks (+/- 2 weeks) from chickenpox exposure</td>
<td>Within 1 month of treatment</td>
</tr>
<tr>
<td>Death Form</td>
<td>Date and cause of death</td>
<td>Immediately upon notification of patient’s death</td>
</tr>
<tr>
<td>Deviation Form</td>
<td>Completed in the event of a deviation from the protocol</td>
<td>Immediately upon discovering deviation</td>
</tr>
<tr>
<td>Withdrawal Form</td>
<td>Used to notify the Trials Office of EITHER patient withdrawal from the trial treatment OR patient withdrawal from all trial procedures, including data collection</td>
<td>Immediately upon patient withdrawal</td>
</tr>
</tbody>
</table>
Ad hoc forms
Serious Adverse Event Form
Pregnancy Notification Form
Pregnancy Release of Information Form

The CRF must be completed, signed/dated and returned to the Trials Office by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within the timeframe listed above. Exceptions to this are the SAE Form and Withdrawal Form which must be co-signed by the Investigator.

Entries on the CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

The PEPtalk2 Treatment Diary, PEPtalk2 Patient Survey; EQ-5D (version as appropriate); and PEPtalk2 Clinician Survey will be used to collect data directly, which may not otherwise be captured in the source data.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

The completed originals should be sent to the Trials Office and a copy filed in the Investigator Site File.

Trial forms may be amended by the Trials Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

11.2 Archiving
It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, patients’ hospital notes, copies of CRFs etc) at their site are securely retained for at least 5 years after the end of the trial or following the processing of all biological material collected for research, whichever is the later. Do not destroy any documents without prior approval from the CRCTU Document Storage Manager.
12. QUALITY MANAGEMENT

12.1 Site Set-up and Initiation
All sites will be required to sign a Clinical Study Site Agreement prior to participation. In addition all participating Investigators will be asked to sign the necessary agreements and registration forms, and supply a current CV to the Trials Office. All members of the site research team will also be required to sign the Site Signature and Delegation Log, which should be returned to the Trials Office. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File and a Pharmacy File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Trials Office must be informed immediately of any change in the site research team.

12.2 On-site Monitoring
Monitoring will be carried out as required following a risk assessment and as documented in the CRCTU Quality Management Plan. Additional on-site monitoring visits may be triggered for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required the Trials Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the PEPtalk2 trial staff access to source documents as requested.

12.3 Central Monitoring
Where a patient and/or parent/guardian (as appropriate) has given explicit consent, sites are required to send in copies of signed Informed Consent Forms for in-house review.

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming Case Report Forms for compliance with the protocol, data consistency, missing data and timing. Sites will be sent Data Clarification Forms requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the main Research Ethics Committee (REC) and the Medicines for Healthcare products Regulatory Agency (MHRA).

12.4 Audit and Inspection
The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are also requested to notify the Trials Office of any MHRA inspections.

12.5 Notification of Serious Breaches
In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial
Sites are therefore requested to notify the Trials Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.
13. END OF TRIAL DEFINITION

The end of trial will be 5 months after last randomisation. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The Trials Office will notify the MHRA and main REC that the trial has ended and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

After closure of the trial with the MHRA the Sponsor is no longer required to notify the MHRA and main REC of changes of Principal Investigator. However, sites should continue to notify the Trials Office of changes in Principal Investigator by completing and returning (where required) an Investigator Registration Form together with a current signed and dated CV.

The Trials Office will notify the MHRA and main REC that the trial has ended at the appropriate time and will provide them with a summary of the clinical trial report within 12 months of the end of trial.
14. STATISTICAL CONSIDERATIONS

14.1 Scheduled Analyses
As this is a pilot study, it will be underpowered to detect any difference in treatment effect between the study arms – and so, unless otherwise specified, analysis will take the form of descriptive statistics on pooled data only, with no formal hypothesis testing to be carried out.

Specific analyses will include:
- summary tables of patient demographic data at baseline
- basic descriptive statistics covering logistical data such as randomisation rates, compliance rates (unpooled data), follow up rates and completion rates for QOL questionnaires
- lists of SAE’s together with treatment allocation
- rates of incidence of VZV (to be looked at unblinded by the Data Monitoring Committee before commencement of the main study) and seroconversion, together with a table of severity scores
- rates of administration of other antivirals
- summary data from the clinician survey
- calculation of the main costs and health-related quality of life implications.

14.2 Sample Size Considerations
As this is a pilot study no formal sample size calculation had been carried out. 50 patients is a reasonable number to obtain the information needed for the design of the main study.

This pilot study will help inform the sample size calculations for the main trial. It is difficult to provide a precise description of the likely sample size assumptions for the main trial in the absence of reliable data (including what would be a clinically acceptable non-inferiority margin) on which to base the assumptions. As the following example demonstrates, it can be difficult to perform non-inferiority trials in rare diseases: assuming a relatively large non-inferiority margin of 10%, and a VZV incidence of 20%, about 450 patients would be needed with a one-sided alpha of 0.05 and 80% power (including allowance for drop-out); if the alpha were to be relaxed the number would be reduced (with alpha=0.1, n=330; alpha=0.2, n=210). From the previous point, a trial of 450 patients should be feasible if the pilot is successful in reaching its accrual target. A smaller trial might also be reasonable as we would be comparing two “standard” treatments, as opposed to evaluating a novel agent, so a lesser degree of “certainty” (i.e. a relaxed alpha) would be acceptable.

Alternatively, rather than designing the trial using conventional criteria (alpha, beta), a likelihood Bayesian approach could be considered in which the probability that one treatment is better than the other by various amounts is given and a clinical decision is made, based on a holistic assessment of all relevant factors (to include efficacy, side-effects, patient acceptability, cost).

14.3 Stopping Rules
As this is a small-scale pilot trial, using standard therapies with familiar safety profiles in their normal paediatric setting, it is not considered appropriate to establish stopping rules for the trial as a whole.

As regards individual patients, the clinician and patient’s parent or legal representative must be aware that the safety implications for VZIG and aciclovir are uncertain where a patient becomes pregnant. In cases of pregnancy, the following information should be kept in mind by the clinician, parent/representative and (if possible) the patient, and an informed decision reached as to the merits or demerits of continuing PEP:
- The relevant safety implications have not been established in controlled clinical trials.
- Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.
- Similarly, there is no evidence that aciclovir suspension or tablets have any effect on female human fertility.
15. TRIAL ORGANISATIONAL STRUCTURE

15.1 Sponsor
This study is sponsored by The University of Birmingham.

15.2 Coordinating Centre
The trial is being conducted under the auspices of the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham, according to their local procedures.

15.3 Trial Management Group
The Trial Management Group (TMG) is composed of the Chief Investigator, Co-investigators and the trial team at the CRCTU. The TMG is responsible for the day-to-day running and management of the trial and will meet by teleconference or in person as required.

15.4 Data Monitoring Committee
Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further patients. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC is scheduled to meet prior to the trial opening to recruitment, when it will confirm the schedule of subsequent meetings. Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the Trial Management Group (TMG), which will convey the findings of the DMC to the MHRA and NIHR. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise patient safety. The trial would also stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community.

15.5 Finance
PEPtalk2 is a clinician-initiated and clinician-led trial funded by the National Institute for Health Research, Research for Patient Benefit programme. It has been adopted by the National Institute for Health Research Cancer Research Network (NCRN) and co-adopted by the National Institute for Health Research Medicines for Children Research Network (MCRN).

No individual per patient payment will be made to Investigators or patients. NHS Trusts will be compensated for their work carried out in relation to PEPtalk2 and there is a budget for travel expenses incurred by participants due to attendance at the follow-up appointment 12 (+/- 2) weeks following VZV exposure.
16. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 1998 and Human Tissue Act 2004) and the International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the main Research Ethics Committee (REC) prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the Trials Office.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians’ responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.
17. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998.

With the consent of the patient and/or parent/guardian (as appropriate), the patient’s full name, date of birth, National Health Service (NHS) number or, in Scotland, the Community Health Index (CHI), address, post code, hospital number and general practitioner details will be collected at trial entry to allow tracing through the Cancer Registries and the NHS Information Centre for Health and Social Care (service formally provided by the Office of National Statistics) and to assist with follow-up via other healthcare professionals (e.g. patient’s GP).

Patients will be identified using only their unique trial number, initials, hospital number and date of birth on the Case Report Form and in correspondence between the Trials Office and the participating site. However patients and/or parents/guardians (as appropriate) are asked to give permission for the Trials Office to be sent a copy of their signed Informed Consent Form which will not be anonymised. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to the Trials Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The Trials Office will maintain the confidentiality of all patients’ data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient and/or parent/guardian (as appropriate) has given explicit consent for data transfer. Representatives of the PEPtalk2 trial team may be required to have access to patients’ notes for quality assurance purposes but patients and parents/guardians should be reassured that their confidentiality will be respected at all times.
18. INSURANCE AND INDEMNITY

University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment.

In terms of liability at a site, NHS Trust and non-Trust hospitals have a duty to care for patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven.

The University of Birmingham cannot offer indemnity for non-negligent harm. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.
19. PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Trial Management Group (TMG) and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.
20. REFERENCE LIST


APPENDIX 1 - WMA DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Recommendations guiding physicians
in biomedical research involving human subjects
Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION
It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES
1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration,
comment and guidance to a specially appointed committee independent of the investigator and the
sponsor provided that this independent committee is in conformity with the laws and regulations of
the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified
persons and under the supervision of a clinically competent medical person. The responsibility for
the human subject must always rest with a medically qualified person and never rest on the
subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the
importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful
assessment of predictable risks in comparison with foreseeable benefits to the subject or to others.
Concern for the interests of the subject must always prevail over the interests of science and
society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every
precaution should be taken to respect the privacy of the subject and to minimise the impact of the
study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless
they are satisfied that the hazards involved are believed to be predictable. Physicians should
cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the
accuracy of the results. Reports of experimentation not in accordance with the principles laid down
in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the
aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may
entail. He or she should be informed that he or she is at liberty to abstain from participation in the
study and that he or she is free to withdraw his or her consent to participation at any time. The
physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly
cautious if the subject is in a dependent relationship to him or her or may consent under duress. In
that case the informed consent should be obtained by a physician who is not engaged in the
investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in
accordance with national legislation. Where physical or mental incapacity makes it impossible to
obtain informed consent, or when the subject is a minor, permission from the responsible relative
replaces that of the subject in accordance with national legislation. Whenever the minor child is in
fact able to give a consent, the minor's consent must be obtained in addition to the consent of the
minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved
and should indicate that the principles enunciated in the present Declaration are complied with.
II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE
(Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.
APPENDIX 2 - DEFINITION OF ADVERSE EVENTS

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.

Comment:
An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Adverse Reaction
All untoward and unintended responses to an IMP related to any dose administered.

Comment:
An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event
Any untoward medical occurrence or effect that at any dose:
- Results in death
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the Investigator***

Comments:
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 patients/event outcome or action criteria.
* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
** Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.
*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Serious Adverse Reaction
An Adverse Reaction which also meets the definition of a Serious Adverse Event.

Suspected Unexpected Serious Adverse Reaction
A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.
A SUSAR should meet the definition of an AR, UAR and SAR.

**Unexpected Adverse Reaction**

An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).

When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
APPENDIX 3 - COMMON TOXICITY CRITERIA GRADINGS

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved:

TRIALS UNIT –

Children’s Cancer Trials Team
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