CLINICAL TRIAL SUMMARY REPORT

Study Title: PEP*talk2*

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

Chief Investigator:	Professor Paul Heath
Sponsor:	University of Birmingham
Sponsor's Protocol No:	RG_12-201
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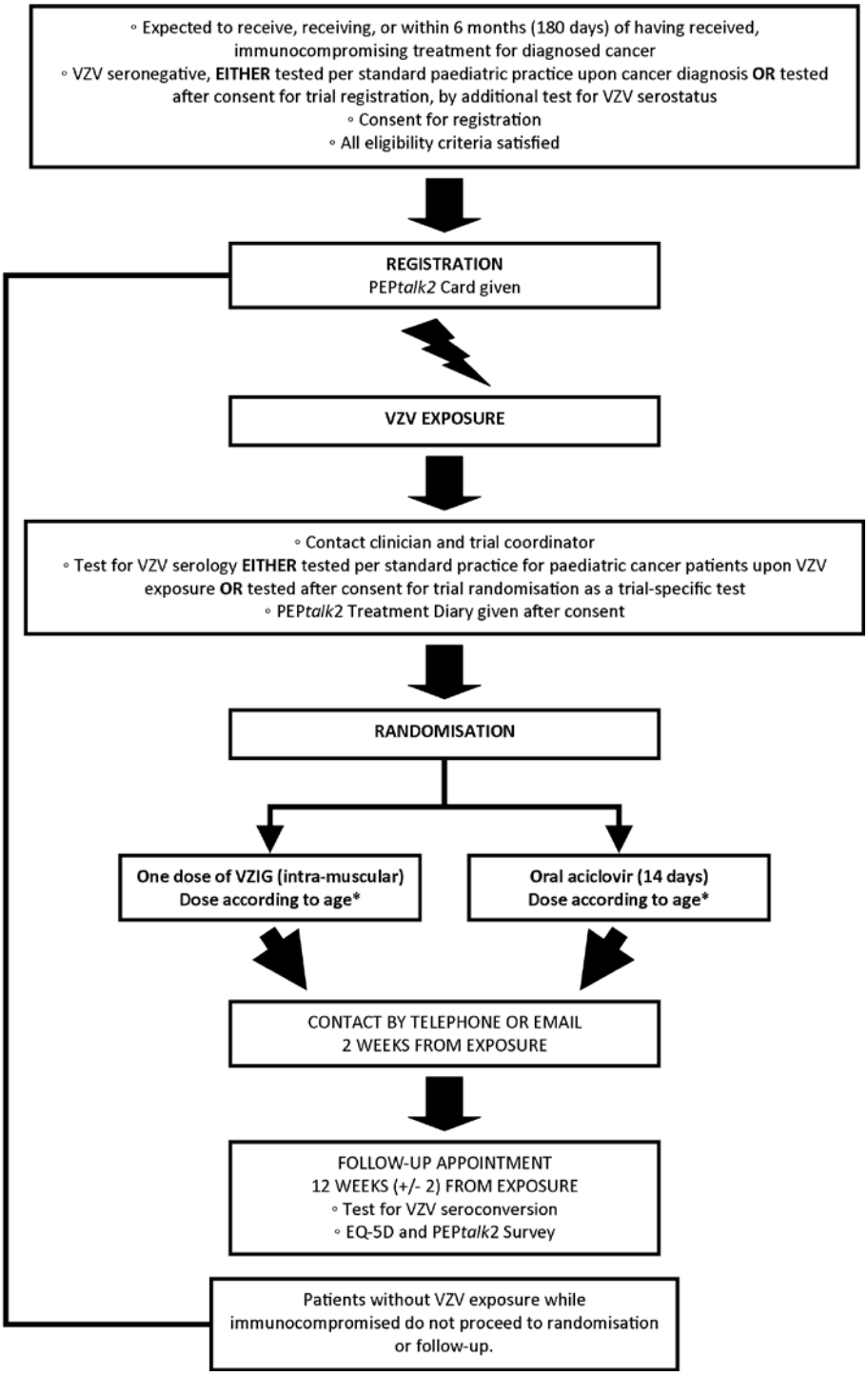
Substantial Amendments:	Amendment 01: 11th November 2013 Amendment 02: 31st October 2013

Details of Investigational Medicinal Products:

VZIG
Varicella zoster immune globulin (VZIG) contains IgG prepared from plasma of donors selected for high titers of antibodies to varicella zoster virus (anti-VZV), and is used to provide temporary passive immunity to VZV.

Aciclovir
Aciclovir is a synthetic nucleoside analogue active against herpesviruses.

Trial Design and Methodology



This pilot study was a multi-centre, randomised controlled trial. It was 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 was planned to randomise 50 children from selected centres over a 12-month period who met the following eligibility criteria:

- Under 16 years of age
- Diagnosed with cancer such that there is a standard expectation of immunocompromising therapy or currently receiving immunocompromising treatment for cancer or within 6 months (180 days) of having received immunocompromising treatment for cancer
- No previous allogenic or autologous haemopoietic stem cell transplantation/rescue
- Negative VZV serostatus result at cancer diagnosis or negative VZV serostatus result within the last three months as assessed locally
- Written informed consent for registration received from parent/legal representative and, where appropriate, written patient assent.

VZV-seronegative children were randomised to receive either VZIG or aciclovir following significant exposure to varicella. Blood for VZV serology was to be taken at the time of exposure and at 12 weeks (+/- 2 weeks) following exposure. For all participants, information on healthcare usage was to be collected. For participants who developed chickenpox, information on disease severity was also to be collected. Patients and their families were given a PEP*talk2* 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 also received an EQ-5D questionnaire to be completed at a follow-up appointment 12 (+/- 2) weeks after exposure).

As PEP*talk*2 had 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 – was obtained at both stages. All parents/guardians and /or patients gave written informed consent for registration and randomisation into the study before any study specific procedures were performed.

Trial Rationale

Justification for patient population

Primary VZV infection usually follows a benign clinical course and significant complications are uncommon in healthy children. By contrast, infection in immunocompromised patients can result in significant morbidity and even mortality. A feasibility study regarding Post Exposure Prophylaxis (PEP) against VZV in children with cancer was carried out by members of the Trial Management Group during 2010. This study confirmed that VZV exposure and disease are frequent and can cause 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 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 acute lymphoblastic leukaemia **(**ALL). Such patients generally require antiviral treatment in hospital as well as interruption to their cancer chemotherapy, and may still become very unwell. Furthermore, having acquired VZV during therapy they become susceptible to its reactivation as herpes zoster (shingles). Varicella prevention is therefore an important goal in this patient population although there continues to be uncertainty about best practice.

Justification for design

The feasibility study conducted by members of the then Trial Management Group (TMG) showed that varicella exposures are frequent but that the approach to PEP in paediatric cancer patients is highly polarised among centres. 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 was 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 was 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, a larger trial could be planned accordingly.

We planned to collect data on children who were 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% and a 30% risk of VZV exposure; 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 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.

Choice of treatment

Subject to VZV exposure being recognised, the relatively 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. However, available data suggest that varicella still occurs relatively frequently following VZIG and, although usually mild, it is occasionally severe or fatal. 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. 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. This study reported very low rates of varicella after nosocomial exposure using 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 (RCPCH) offered aciclovir as an alternative to VZIG in the immunocompromised child. 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. There have been no reported cases of severe/fatal varicella following the institution of this change, but neither has 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. 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, PEP*talk2* participants who had a significant VZV exposure were randomised after the exposure to receive PEP in the form of either VZIG or aciclovir. VZIG was to be given by intramuscular injection – dose depending on age – within 10 days of exposure. High dose oral aciclovir commenced 7 days after exposure and was given for 14 days.

Objective

Primary objectives:

- 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.

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.

Recruitment

The recruitment target for the trial was 50 randomised patients.

Opened sites:

- Bristol Royal Hospital for Children, Bristol - opened 27th June 2014
- Croydon University Hospital, Croydon - opened 13th August 2014
- Leeds General Infirmary, Leeds - opened 9th May 2014
- Royal Manchester Children's Hospital, Manchester - opened 27th June 2014
- University Hospital Southampton, Southampton - opened 8th August 2014
- St Georges Hospital, University of London - opened 11th June 2014

Number of patients expected:	50	randomised patients
Number of patients registered:	32	
Number of patients randomised:	3	
Number of patients screened:	482	

Results

Six centres were opened, 482 patients were screened for eligibility, 32 subjects were registered and 3 patients were randomised following VZV exposure. All 3 were randomised to receive aciclovir and all 3 completed follow-up according to protocol.

There was a steady rate of screening over the 13-month trial period, although one site registered the majority of patients (Leeds). Screening commenced at different times with 1 sites screening throughout the 13-month period, 3 sites for 12 months and 2 sites for 11 months. Overall 71 months of screening occurred across the 6 sites.

A consistent proportion of patients were not eligible for registration because they were seropositive (ranging from 65-70% by month, overall 69.9%). Those with indeterminate results were also not eligible for registration and this proportion declined over the first 6 months of the course of the trial, from 20% to 13%, and then remained steady at 11-13% for the remainder of the trial (overall 12%). The proportion of patients that were seronegative and therefore eligible for participation (n=76, 16%) was also consistent over the study period (12% for the first month and then 14-17% by month). Seronegativity status varied by age: 50% in 2-4 year olds, 21% in 5-7 year olds, 5% in 8-10 year olds and 8% in >10 years of age. The median age of seronegative patients was 3.8 years.

The % of seronegative patients that were registered after screening (n=32, 42%) increased quickly over the first 3 months of the study from 19 to 40% and was then consistently around 40% per month (overall 7% of those screened were registered, 32/482). The median age of the registered patients was 3 years (range 1-11).

For those who declined to be registered (n=44, 58%) the major reason given was the distance of travel to the trial site (n=23, 52%). This was particularly so for Bristol. The other main reasons were the need for additional oral medication (n=6, 14%) and the need for additional blood samples (n=8, 18%). Personal communications with local staff indicated that families who declined due to the need for further oral medication, declined as the patient(s) no longer had nasogastric tubes and had struggled with oral medications previously. Another reason given for declining was that the patient was back at school and taking oral medications during school time was an issue for them.

Three patients were randomised to receive PEP (9% of registered patients); occurring in July 2014, September 2014 and April 2015; two were at the Manchester site with the third at Southampton. In two cases the exposure to VZV preceded registration, and randomisation was then undertaken on the same day as registration. In the other subject the interval between registration and randomisation was 50 days. The age of the 3 patients was 5.8, 6.1 and 6.8 years, in two the source of contact was a sibling and in the other it was a source outside the household. The three were all randomised to receive acyclovir and all three were assessed as being compliant with the full course. There were no cases of VZV among the patients and none seroconverted between exposure and the 12-week follow-up.

Quality of Life (QOL) questionnaires were returned for all patients at baseline, for 2 patients at the 14 day and for 2 at the 12-week time points. EQ5D-3L is calculated as an index score with a higher score representing a better quality of life. For one subject the score was 1 throughout, for one it was 0.76 at baseline and 0.16 at 12 weeks (no 14 day return) and for the other it was 0.59 at both the baseline and 14-day assessment and there was no 12-week assessment. EQ5D-VAS is a measure of

the patient's self-rated health, this score ranges from 0 to 100, with a higher score representing a better quality of life. One subject recording a similar (high) score at all 3 time points (92, 85, 92), one a small decline from baseline to last time point (80, not done at 14 days, 73) and the third subject recorded the same score at the first 2 time points (60) and then did not submit a score for the 12-week time point.

Clinician surveys.

Feedback was recorded from all participating clinicians (n=8). All respondents indicated that the quality of information they were given about the study was moderately good or above, 3 of 3 responded that randomisation went smoothly, all 8 indicated that study documentation, as well as research staff responses, was moderately good or above and 7 of 8 that the experience of participating was moderately good or above (1 respondent indicating slightly good). Specific feedback was very complimentary about the communication and support from the CRCTU, that the patient information sheet could be condensed further, that the effort taken in registering patients should be recognised in terms of portfolio accruals, that shared care centre involvement was important and that routine practice currently does not require serological screening of patients with a history of VZV. In terms of enhancing clinician interest in a future definitive trial, it was recommended that presentations at Children's Cancer and Leukaemia Group (CCLG) annual meetings and using postcards for patients with study details were most favoured, while site visits by the research team and clinician desktop reminders were least favoured.

Parent surveys.

The 3 parent respondents were fairly uniform in their assessment of the trial with all indicating that study procedures were excellent (and 1 indicating fairly good for treatment diary use). Their main indicated reasons for agreeing to take part were to help decide further treatment for other children (2/3) and for 1, the possibility of having oral syrup rather than an injection.

Discussion.

The main objective of this pilot study was to determine the likely rate of patient randomisation and to facilitate sample size calculation, in order to inform the design of a larger trial addressing the issues around post exposure prophylaxis in this population. It was estimated that if, for example, the pilot study was 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 was realistic and could recruit around 200 patients. This was seen as achievable in the UK network. If found to be necessary the trial size could also be increased further, but an international consortium would then likely be required to achieve this. This main objective was therefore achieved.

The pilot study recruited only 3 patients from 6 centres. This suggests that recruitment of sufficient numbers to a definitive (and similarly designed) trial would not be achievable. As intended, the pilot study has allowed us to identify a number of reasons for this low rate of recruitment and indeed, with this knowledge, a number of these could now be avoided in the design of a further trial - but nevertheless, a different approach to addressing the issues around PEP will likely be needed.

Only 6, rather than 7, sites were able to participate in the pilot study and of these only 4 were able to participate for the full trial period. Assuming that this has a direct bearing on recruitment then if all sites had participated fully (78 months rather than

71 months), the numbers screened and numbers randomised would have been 557 and 3.3 respectively. If 7 sites had participated (91 months) this would be 617 and 3.9 respectively. Choice of sites might however be critical as one site dominated in terms of registration (15) thus 7 similar sites could have registered 105 patients (and thus randomised 10 patients). These numbers are still significantly lower than originally proposed but other factors should also be considered.

An eligibility criterion was omitted from the original protocol i.e. being up to 6 months post treatment. This was introduced as a later amendment and may have had some impact (likely small) on the recruitment rate.

The rate of seronegativity (16%) was lower than predicted (50%). This was originally estimated by comparing the age distribution of cancer and leukaemia in the UK with the VZV age seroprevalence in the UK. An important factor here was the high rates of “indeterminate” results (around 13%). Not to have incorporated this in the protocol was an important omission as in practice such cases should be considered as potentially susceptible. Additionally, there was also a clinical practice not to assess status in those with a history of VZV, this should also have been addressed in the protocol and repeat serology obtained on such children. We and others have shown that such children can still be seronegative.

The reasons given for not agreeing to participate are important and this knowledge would allow adjustments to be made to the protocol. For example, it would be important to ensure that all shared care hospitals of the major recruitment sites are also engaged in the study so that travel for research patients is minimised.

Concern was evident regarding the need for blood samples and these could be reduced in a future trial, for example the need to repeat serology again at randomisation.

During the trial period, there was a lower rate of VZV exposure (10%) than originally predicted (20%). Although accurate data on the rates of VZV exposure and disease are not available for UK children with malignancy, a 20-30% risk of varicella exposure during a child’s mean 2.5 years of maintenance therapy for ALL had been estimated from one study. In another study of 86 children followed through the duration of ALL treatment there were 26 episodes of chickenpox and herpes zoster, of which 17 occurred during maintenance therapy. There is an indication that exposure of the general population during this time period was also lower than in other years. Clearly, had we identified susceptible children earlier in the trial period and then followed them for a longer period of time (as could be done in a definitive trial); this would have allowed greater exposure to VZV and minimized the impact of seasonal variations in VZV exposure.

Among the secondary objectives were to create interest in and support for the study amongst paediatric oncologists. The survey of participating clinicians was in fact supportive of the approach taken and of the trial processes.

Given the limited recruitment to this pilot study, it would likely be difficult to undertake a conventional non-inferiority trial of these two forms of PEP. However, given that the trial would be comparing two standard treatments, it would be appropriate to use a Bayesian approach to the trial design. By designing the trial in this way, we would be able to compare the observed data from the two treatment arms and make an informed decision regarding the treatments without making any assumptions in the design as to whether it was a superiority or a non-inferiority trial.

Is a definitive non-inferiority trial still required? In the UK, we do not have a routine varicella vaccine program in place, in contrast to a number of other industrialised countries. Such countries have seen a dramatic decline in the incidence of varicella in their childhood population in both their vaccinated and unvaccinated populations (through herd immunity). Herd immunity is particularly important to the population studied in PEP*talk2* because they would not be routinely offered the live attenuated varicella vaccine anyway, although this strategy could again be explored. VZV remains an issue in children with cancer in all countries without routine immunisation programmes. The UK Joint Committee on Vaccination and Immunisation (JCVI) is currently reviewing the status of the VZV vaccine and it may be that this will change; even so the impact on this population would not be felt for some time. The equipoise between aciclovir and VZIG as the best way of providing post exposure prophylaxis also remains. No substantial data have been published in the interim that suggest one is superior to the other. One study only (published in Spanish), refers to the experience in one centre with both options available. Following exposure to varicella, susceptible patients (39% haematology/oncology) received aciclovir as prophylaxis in 61% (n: 65); immunization in 10% (n: 10); and gamma globulin in 1 patient. No adverse effects were observed in relation to the different prophylaxis measures. No secondary cases were observed at 30 days.

Other ways of comparing these interventions in clinical practice might now be possible, such as through the use of large observational data sets; this option should be reviewed.

Toxicity

No serious adverse reactions (SARs) were reported during the course of the trial.

There have been no SUSARs, and the risk/benefit evaluation has not changed over the duration of the study.

Abstracts

There have been no abstracts.

Publications

There have been no publications.

Conclusion

We conducted a pilot, randomised controlled trial of post varicella exposure prophylaxis in children with leukaemia, in order to determine the likely rate of randomisation and to facilitate sample size calculation for a definitive trial. Over a 13-month period we screened 482 children, registered 32 and randomised 3 children, from among 6 trial sites. A number of issues were identified that could be used to modify the design of a definitive trial but overall our experience suggests that the necessary sample size is not achievable using this recruitment strategy. Other options for defining the best means to protect such children against VZV should be explored.

Study End date: 30th June 2015

Declaration

Signature of Chief Investigator:	
Print name:	Professor Paul Heath
Date:	17-Jan-2017

This report was prepared by the Chief Investigator and the Cancer Research UK Clinical Trials Unit (CRCTU) on behalf of the Sponsor.

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