NETSCC, HTA

23 October 2009

THE UNIVERSITY of York

PROTOCOL FOR: Cryotherapy versus salicylic acid for the treatment of verrucae: A randomised controlled trial.

Protocol version 10

16 Oct 2008

Funded by the HTA

Prof David Torgerson_____

Prof Ian Watt _____

Principal Investigator_____

AMENDMENTS TO PROTOCOL

A Protocol Version 2 29 September 2004

Change in concentration of salicylic acid from 60% to 50% Verrugon.

B Protocol version 3 26th July 2006

In light of the changes made due to obtaining funding from the HTA and after discussions held with the Trial Management Team the following changes were made:

- Additional background information added
- Clarification of primary and secondary outcomes
- Additional exclusion criteria added
- Clarification of treatment details for both salicylic acid and cryotherapy
- Additional recruitment strategies included
- Addition of web-based randomisation service added
- Notification of participant's GP involvement in the study included
- Clarification of non recruitment and use of 'Ineligible Patient Form'
- Clarification of ethical arrangements, reporting and monitoring adverse events and obtaining informed consent
- Additional section on treatment of missing data

C Protocol version 4 21st November 2006

In light of the advice from the Trial Steering Committee held on the 20th September 2006 and discussions held with the trial management team it was decided to

- Clarify the secondary outcomes and the economic analysis
- Add additional exclusion criteria
- Clarify treatment details for patients presenting with more than one verrucae and the regimen for cryotherapy treatment
- The influence of prognostic variables on the primary outcome will be also be investigated.

D Protocol version 5 4/5/2007

In light of the advice from the Trial Steering Committee held on the 22 March 2007 and discussions held with the trial management team it was decided to:

- Clarify the exclusion criteria to read 'oral' corticosteroids, not corticosteroids
- Further clarification to cryotherapy regimen: debridement prior to treatment now no longer necessary for the trial but if carried out should be done as per normal practice eg scalpel, file and a record kept of the method used; method of application of liquid

nitrogen is changed to normal practice eg spray probe or cotton bud if there is a choice then spray should be used; time interval between treatments to 2/3 weeks as there is no evidence to suggest there is a significant difference in effectiveness in treatments 2 or 3 weeks apart, and no further benefit from treating more than 4 times.

- We will ask participants who did not attend their outcome assessment appointment at 12 weeks if they would be able and willing to take a digital photo of their foot/feet and send it to the York Trials Unit EverT email account
- Clarification that data on adverse events will be collected by patient self-report
- Minor clarification to the economic analysis (patient perspective was missed out)
- Minor clarification to the reporting of adverse events
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E Protocol version 6 July 2007

- Clarification that Professor David Torgerson is the Chief Investigator and Prof Ian Watt as Co-Chief Investigator.
- Additional exclusion criteria of patients with neuropathy
- Additional information about the storage and dispensing of Verrugon and supply of liquid nitrogen
- Adverse event/reaction reporting. Additional information included about reporting time of adverse events/reactions, duration of reporting, out of hours contact

F Protocol version 7 5th September 2007

- Additional sites of Camden and Sefton PCT, Brownlow and Springfield Practice added.

G Protocol version 8 22nd November 2007

- Additional sites included: Islington PCT and Dr Mittal

H Protocol version 9 20 February 2008

- Additional site included: Sheffield PCT and additional recruitment strategies, clarification of treatment of missing data

I Protocol version 10 16 Oct 2008

- Space for signature of Principal Investigator added to front page
- Amended to read Verrugon is to be applied ‘once’ daily rather than daily
- A sample of the Verrugon label is included

- Clarification that patients should see their out of hours GP if a problem occurs outside of normal working hours
- Participants who attend their 12 week outcome assessment to be sent £20 to cover any expenses incurred
- Patients to be sent an unconditional £5 with the 12 week questionnaire, to cover expenses incurred when completing questionnaires.
- Clarified wording to read "If a clinician feels that the potential participant is unable to give informed consent, then they would not be eligible to take part in the study."
- Clarified wording to read "This sample size will also enable us to show that"
- Clarified to read "giving a total of 270 participants"
- Camden and Sefton PCT removed from list of sites. Claughton Medical Centre (Birkenhead, Wirral), Woodplumpton Road Surgery (Fulwood, Preston) and Arlington Road Surgery (Eastbourne) added as new sites.
- Amended Project Timetable to reflect approved extension of project

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1. BACKGROUND

Verrucae or plantar warts are a common, infectious and sometimes painful problem. Using incidence figures from the 4th National Morbidity Survey (1991-92)[1] an unpublished economic decision model assessing the effectiveness and cost-effectiveness of salicylic acid and cryotherapy has estimated that almost 2 million people see their GP per year about cutaneous warts at a cost of at least £40 million per annum. Although most verrucae will spontaneously disappear without treatment many patients seek treatment to remove a verruca due to it being painful or because they are being prevented from doing sports.

A recent systematic review conducted by the Cochrane Skin Group assessed the effects of different local treatments of cutaneous, non-genital warts in healthy people[2]. This review highlighted the uncertainty with respect to the optimal treatment of verrucae. There was however, some evidence from six trials to suggest that treatment with salicylic acid was more effective than placebo/no treatment, odds ratio 3.91 (95% confidence interval 2.40 to 6.36). Freezing warts using cryotherapy is widespread (an unpublished survey of GP practices in Nottingham found that 71% offered cryotherapy for the treatment of warts in 2002 – Thomas, personal communication). Many patients experience unpleasant side effects such as pain and blistering during cryotherapy treatment, yet the same review found no evidence to suggest that it is more effective than treatment with topical agents such as salicylic acid. Only two trials were identified which compared salicylic acid and/or lactic acid with cryotherapy, but there was no difference in the efficacy between the treatments (OR 1.15, 95% CI 0.72 to 1.82). However, both trials were reported as low quality, due to unclear allocation concealment, inadequate blinding procedures, small sample sizes and inappropriate follow-up and analysis.

Since verrucae are seen as a ‘minor’ condition few trials have been funded in this area. In addition to this of the 52 trials included in the systematic review only 3 were classed as high quality and 75% were classified as low quality. There is a need therefore, for a high quality randomised controlled trial with a cost effectiveness analysis to ascertain which is the best approach for the treatment of plantar warts.

2. RESEARCH OBJECTIVES

Primary objective

To compare the clinical effectiveness of cryotherapy versus salicylic acid for the treatment of plantar warts in terms of the complete clearance of all verrucae as observed on digital photographs taken at baseline and 12 weeks and assessed by an independent health care professional (eg podiatrist, GP, Practice nurse). Blinded health care professional assessment will be used if for some reason the digital photograph is not interpretable. 'Clearance' of verrucae will be defined as being the restoration of normal skin upon close inspection, as assessed by the health care professional.

2.2 Secondary objectives

To compare the cost effectiveness of cryotherapy versus salicylic acid for the treatment of plantar warts in terms of the complete clearance of all verrucae. To assess the acceptability of the two approaches and to investigate

- Self-reported time to clearance of verrucae
- Recurrence/clearance of verrucae at six months

In addition to this, side effects of treatment, pain intensity after treatment, use of painkillers, restrictions to lifestyle due to having the verruca, treatment details will be recorded. Patient satisfaction with the treatment and the number of verrucae will also be recorded.

3. DESIGN

The proposed study is a pragmatic, multicentre, randomised controlled trial (RCT) with equal randomisation. Patients with verruca will be allocated equally between the two treatment groups, namely: 50% salicylic acid paste and cryotherapy using liquid nitrogen.

4. ELIGIBILITY

4.1 Inclusion Criteria

Patients will be eligible if all of the following criteria apply:

- The patient has a verruca that in the opinion of the health care professional is suitable for treatment with both salicylic acid and cryotherapy.
- Are aged 12 years and over

4.2 Exclusion Criteria

Patients will be excluded if any of the following criteria apply:

- Are currently in a trial evaluating other treatments for their verruca
- Have impaired healing eg due to diabetes, peripheral vascular disease or any other condition which means the patient has impaired healing
- Patients that are immunosuppressed eg have agammaglobulinaemia, or are currently taking immunosuppressant drugs such as oral corticosteroids
- Are unable to give informed consent
- Are currently on renal dialysis
- Have cold intolerance eg Raynaud's syndrome or cold urticaria
- Have any of the following conditions - blood dyscrasias of unknown origin, cryoglobulinaemia, cryofibrinogenaemia, collagen and auto-immune disease
- Patients with neuropathy

5 TREATMENT DETAILS

Participants will be randomised equally between the two arms: daily self-treatment by the patient with 50% salicylic acid; cryotherapy using liquid nitrogen delivered by the health care professional (for example podiatrist, practice nurse, General Practitioner). If a patient

presents with more than one verruca, then the Health Care Professional should treat the verrucae as they would in normal practice.

A 'no treatment' arm will not be included in this study. There are a number of reasons for this. Firstly, the systematic review showed that salicylic acid is more effective than 'no treatment', whilst failing to find any evidence for the effectiveness of cryotherapy. Therefore, the important clinical question is whether the use of cryotherapy is superior to that of the standard effective treatment. Secondly, a 'no treatment' arm may lead to bias due to resentful demoralisation, particularly in those patients where the verrucae are painful, longstanding and resistant to previous treatment.

5.1 Daily self-treatment by the patient with 50% salicylic acid paste - Verrugon

- At the first appointment the health care professional will instruct the patient and/or their parent or guardian if appropriate, on its use. Thereafter, it will be applied **once** daily for a maximum of 8 weeks as per the manufacturer's instructions as follows:
- The self-adhesive ring should be fixed with the hole over the verruca.
- Squeeze a little Verrugon ointment into the hole and directly onto the verruca.
- Remove backing paper from plaster.
- Cover ring completely with plaster. Seal into position.
- Repeat treatment daily after gently pumicing or filing off the dead part of the verruca

Patients will be asked to return all the Verrugon tubes they have received during the duration of the trial to the health care professional at their 12 week appointment. The health care professional will then weigh the tube to determine how much Verrugon has been used over the 8 week period.

Only those patients enrolled in this study may receive the Verrugon. The 50% salicylic acid will be provided by the sponsor and will be dispatched to the treatment centre to be dispensed to participants by either a podiatrist, doctor nurse prescriber, pharmacist, other qualified health care practitioner or under a patient group directive. Drug accountability is a responsibility of study site personnel and overall drug accountability records will be kept to provide information on stock, dispensing and drug returns.

The salicylic acid should be labeled as per the labeling requirements for investigational medicinal products used in clinical trials which come under requirements of Directive 2001/20/EC and the Medicines for Human Use (Clinical Trials) Regulations 2004 which implement the Directive and came into force on the 1 May 2004. A sample of the labeling is given here:

Verrugon ointment 50% salicylic acid.
Trial EUDRAct number 2004-000905-24
Investigator: Name of investigator
Directions for use: as directed by the instructions give by the manufacturers.

Patient Name

Patient ID

Batch Number Expiry date Date of dispensing

Name and address of podiatry school/podiatry clinic supplier

Keep out of reach of children For clinical trials use only

Verrugon should be stored in a secure area, out of direct sunlight and below 25 degrees centigrade. All unused study drug, including undispensed supplies and supplies returned by the patient will be retained until the end of the study.

5.2 Treatment with cryotherapy using liquid nitrogen delivered by the health care professional

Although not necessary for the trial, sometimes it is the normal practice to debride prior to treatment with liquid nitrogen. If this is the case then the callus surrounding the verrucae will be debrided according to normal practice (eg with a scalpel, file, or not debrided at all) with any haemorrhages stopped by digital pressure only. The tissue surrounding the verruca will be prepared according to normal practice (eg unmasked, or masked with, for example vaseline). Liquid nitrogen will then be applied according to normal practice (eg spray, probe or cotton bud). If there is a choice in the method of application, then a spray should be used. The health care professional should freeze the tissue until they are satisfied that the tissue has been frozen adequately (this will be about 10 seconds if using a spray). 75% silver nitrate

should **NOT** to be applied to site. If the health care professional believes the area surrounding the verruca should be padded after treatment, this will be done according to normal practice eg padded with 7mm felt cavitied padding. The patient will be advised to keep the area dry for 24 hours and that the area maybe uncomfortable as the treatment removes infected skin by causing a blister. If the area is very painful the patient will be recommended to use the type of painkiller they would use for a headache, and as per instruction on the packet. The health care professional will then re book for the next treatment 14 or 21 days later. On the patient's return the sequence should be repeated up to a maximum of four treatments.

The recruiting site will use the equipment and liquid nitrogen used in normal practice to deliver cryotherapy treatment or will under prior agreement with the York trials unit be provided with the equipment. Storage of liquid nitrogen should comply with the current health and safety guidelines.

It is anticipated that some patients will request cryotherapy to be stopped. If the health care professional is not satisfied sufficient freezing has taken place then Verrugon will be offered as the second line treatment. Treatment details for both groups will be collected via questionnaire from the health care professional carrying out the treatment along with an assessment of how painful the treatment was (on a scale of 0 to 10) at the first visit. All participants will be given a follow-up appointment at 12 weeks to assess whether the treatment had been successful or not.

If required, patients in both groups will be able to book a 'fast-track' appointment to see their health care professional if they are concerned about adverse reactions to the treatment. If the patient has a problem with their verruca treatment outside of normal working hours, they will be advised to see their out of hours GP service.

In order to standardise the study prior to commencement the health care professional will receive a Podiatry handbook that will include the following documentation:

- Brief background and aims of the trial
- Inclusion/exclusion criteria

- How to randomise using the York Trials Unit randomisation service which will provide a patient ID number and treatment group
- Protocols for both treatments
- Documentation/forms used in the trial eg randomisation forms, questionnaires, adverse event reporting, ineligible patient forms
- Discuss possible 'Frequently asked questions' participants may ask about the trial
- Give contact details of the researchers at York University

We will also run a one-day training course.

6 RECRUITMENT AND RANDOMISATION

6.1 Recruitment

Potential participants for this trial will be identified by the health care professional from either GP referrals or self-referrals received by the Podiatry Schools, podiatry clinics or practice clinic for the treatment of verrucae. In order to facilitate recruitment, after consultation with the local clinics to ensure unmanageable caseloads do not arise, the following strategies may be adopted to increase the number of patients presenting to the clinics:

- Approach GPs in the area requesting them to directly refer patients presenting with a verruca to the podiatry clinic for treatment.
- We will directly advertise for participants eg within GP surgeries and local swimming pools. We will also advertise for participants at local libraries; in local newspapers; University press releases, local radio and tv stations; in the following local NHS departments: dermatology clinics, outpatient departments, A and E and podiatry departments, staff canteens, walk-in centres; at local occupational health departments in large employers near recruiting sites; in large stores such as supermarkets near recuiting sites; at professional development update days run by the podiatry schools and at local private podiatry clinics.

- Approach secondary schools within the area asking them to send information about the trial to all students. We will also approach local scout, guide, adventure scout, sea and army cadets air training corps and boy's/girl's brigades asking them to give out information about the trial to all members of their group.
- We will approach the University of Bradford and ask if they will post information about the study on their website and noticeboards due to it's close proximity to the University of Huddersfield recruiting site.
- We will advertise for participants on local community websites, eg those run by the local Borough and County Councils, local PCT websites and on the EverT trial website.

These patients will be sent an appointment to attend for assessment/treatment along with a recruitment pack and will be given a minimum of 24 hours to consider participation in the trial. The recruitment pack will contain:

- An invitation letter, including contact details for the local health care professional and trial co-ordinator so that potential participants can contact them to discuss any queries they may have regarding the trial.
- An appropriate patient information leaflet(s), an 'adult' information sheet will be sent to participants aged 16 and over. Participants under the age of 16 will receive two information sheets, one designed for children under the age of 16, the second for their parent/guardian.
- Baseline questionnaire
- Consent form

6.2 Randomisation

Those patients that return the baseline questionnaire and indicate that they are willing to take part will be assessed for inclusion in the study by the health care professional when they attend for their appointment. The health care professional will obtain written consent from all patients/and their parent if required, who are willing to participate prior to the patient being randomised. The York Trials Unit will notify the patient's GP of their involvement in

the study. After consent and before randomisation the health care professional will collect a digital photograph of the verruca.

The health care professional will randomise the patient by either phoning the York Trials Unit remote telephone randomisation service (free phone number) or using the web-based programme. Patients will be allocated to either of the two treatment arms in a 1:1 ratio. Participants will then receive the allocated treatment at that appointment. If at the end of the study the verruca is still present and the participants requires further treatment, the health care professional will consult with the patient as to the best course of action.

Patients who do not wish to take part in the trial or those who wish to opt out will revert to usual care. The health care professional will discuss alternative methods of treatment used within the department with the patient and once a course of treatment has been agreed on, the health care professional will treat and organise further appointments as required.

6.3 Non recruitment

The Health care professional will be asked to complete an "Ineligible Patient Form" for those patients who wished to take part in the trial but were ineligible to do so. These forms will be returned to the York Trials Unit. Information collected will be all reasons patients not eligible, DOB, gender, type of wart and date of consideration for trial entry.

7. OUTCOMES

7.1 Primary outcome

The primary outcome will be complete clearance of all verrucae as observed on digital photographs taken at baseline and 12 weeks and assessed by an independent health care professional. Blind health care professional assessment will also be assessed and will be used if for some reason the digital photograph is not interpretable. 'Clearance' of verrucae will be defined as being the restoration of normal skin upon close inspection, as assessed by the health care professional.

Participants who attend their 12-week outcome assessment will be sent £20 to cover any expenses incurred when attending this appointment.

Participants who do not attend their 12-week outcome assessment appointment will be written to, to determine whether they have a digital camera and if they would be willing to take a photograph of their foot. Those participants who agree to take a photograph will be asked to complete a colour card, which has the participant's ID number on it and the date the photo was taken. The photo will then be sent by email to the York Trials Unit's EverT email account.

Participants may be sent the following reminders

- To attend their final follow up appointment at 12 weeks approximately one week before hand
- To complete follow-up questionnaires, two weeks after the initial questionnaire sent
- At week 7, to stop treatment at week 8 for those assigned to the salicylic acid group
- Weekly to return their tear-off slip when their verruca has gone.

The format of this reminder will either by post, email or text as per the participant's preference.

7.2 Secondary outcomes

- Self-reported clearance of verrucae at six months will be assessed by either patient postal or web-based questionnaire according to the participant's preference.

- Self-reported time to clearance of verrucae will be assessed by either patient postal or web-based questionnaire according to the participant's preference.

In addition to this side effects of treatment, pain intensity after treatment, use of painkillers, restrictions to lifestyle due to having the verruca and treatment details will be recorded and assessed by patient postal questionnaire, which will be sent at 1 and 3 weeks after randomisation. The questionnaire will also include a section for the patient to complete and return to the York Trials Unit once the patient believes their verruca has been cured. The format of this questionnaire will be either paper or web based according to the participant's preference.

Patient satisfaction with the treatment will be recorded by either patient postal or web based questionnaire at 1, 3 and 12 weeks according to the participant's preference. All participants will be sent an unconditional £5 with the 12 week questionnaire in recognition of their commitment to the study and to cover any expenses incurred in completing the questionnaires.

The influence of prognostic variables on the primary outcome (clearance at 12 weeks) will be investigated. Such variables will include age, type of wart, gender and duration of current wart. The variables to be included will be finalised before any analyses are performed.

Economic evaluation: The Economic evaluation will be carried out from the perspective of the UK health care provider, the National Health Service over a time horizon of 12 weeks and the patient.

Resource data: Data will be collected on the volume of participant access to NHS staff and cost of treatments used during the trial. The number of visits each participant makes to the podiatrist or the health care professional for wart treatment, will be assessed using a participant-completed questionnaires sent at 12 weeks. The use of over the counter verrucae treatments, will be assessed by patient postal questionnaire at 12 weeks.

Health outcomes: We will assess the number of verruca free days for each participant using patient self-reported time to clearance of verrucae.

Cost effectiveness analysis: We will carry out a cost effectiveness analysis as detailed in section 10.4

Data on adverse events will be assessed by the number of visits the participants makes to a doctor or health care professional, and notification of adverse events by the health care professional treating the patient or self-report by the participant

8 ETHICAL ARRANGEMENTS

We are aware that children are considered a vulnerable group. However, we do not anticipate any major ethical issues with the proposed study since both treatments under investigation are currently used within normal practice to treat children with verrucae and Verrugon is licensed as an over the counter treatment.

8.1 Adverse events/adverse reactions

The health care professional will routinely record any serious and non-serious adverse events/reactions, which occur during the course of the trial on a serious or non-serious adverse event/reaction form. An assessment of the seriousness, causality and expectedness of the event/reaction will be undertaken. Participants should be asked at each trial visit about hospitalisations, consultations with other medical practitioners, disability or incapacity or whether other relevant adverse events have occurred. The adverse event/adverse reaction reporting period for this trial begins when the patient is randomised into the study and ends 6 months after the date of randomisation. All adverse events and reactions should be followed up until they are resolved or the patient's participation in the trial ends. In addition serious adverse reactions assessed by the investigator as possibly related to the investigational product should continue to be followed even after the patient's participation in the trial is over. Such reactions should be followed until they resolve or until the investigator assesses them as 'chronic' or 'stable'. Appropriate on-going care will be arranged through the appropriate services. Resolution of such events is to be documented on the serious adverse event/reaction form.

Fatal or life-threatening Suspected Unexpected Serious Adverse Reactions (SUSARs) will be recorded and reported to the MHRA, Ethics Committee and Data Monitoring Committee within 7 days of knowledge of such cases. In each case relevant follow-up information should be sought and a report completed as soon as possible. This should be sent to the CA and the Ethics Committee within an additional eight days. All other suspected unexpected serious adverse reactions will be reported to the DMEC, MHRA, and trial sponsor and ethics committee within 15 days of first knowledge.

Once a year a list of all suspected serious adverse reactions, which have occurred over the period, and a report of the subject' safety will be provided to the MHRA.

The known side effects of treatment associated with treatment with salicylic acid and cryotherapy are: pain, blistering, irritation to the skin, burning sensation, bleeding, scarring, infection and in some cases allergic contact rash may occur in some people.

8.2 Informing trial participants of possible benefits and risks of intervention

All trial participants will be provided with a patient information sheet prior to their giving informed consent. The information sheet will outline fully the potential benefits and risks of being involved in the trial. The health care professional will inform the participant if new information comes to light that may affect the participant's willingness to participate in the trial.

8.3 Informed consent

Participation in the study will be entirely voluntary and written consent will be sought. All data will be treated with the strictest confidence.

For those participants under the age of 16, the parent/guardian will be asked to give written consent along with assent of the child. The researcher will at all times consider the explicit wish of the minor if they are capable of forming an opinion and assessing the information provided. This will apply not only to the wish of a minor to refuse to take part, but also to withdraw from the trial at any time. Where the parent is competent to decide for their child but unable to read or write, an impartial witness will sign the consent form to say that the information sheet has been read to the parent and verbal consent has been given.

If a clinician feels that the potential participant is unable to give informed consent, then they would not be eligible to take part in the study.

8.4 Proposed time period for retention of trial documents

Paper copies of the relevant trial documentation from the study will be held in a locked room for a period of 9 years at the University of York (i.e, until the youngest participant is aged 21 years), whilst electronic copies will be held indefinitely.

9 STATISTICAL CONSIDERATONS

9.1 SAMPLE SIZE

The Cochrane systematic review found only one small trial directly comparing the effectiveness of a chemical treatment, salicylic acid, with cryotherapy in patients with warts on their feet alone. This poor quality study found a 58% cure rate among the patients allocated to cryotherapy compared with 41% among those treated with salicylic acid. This difference of 17% was not statistically significant. The overall cure rates from this study are smaller than those observed in two placebo controlled trials of salicylic acid, both of which reported cure rates of 85% for active treatment, possibly because more resistant verrucae were included in the study comparing cryotherapy with salicylic acid.

In this study we have decided to power the trial to show a 15% difference in effectiveness. We therefore, will recruit sufficient patients to give us 80% power (5% two sided significance) to show a difference in cure rates of 70% versus 85% at 12 weeks after treatment. This will require 120 patients in each group after allowing for a 10% drop-out rate we will require 133 in each treatment group (i.e. 266 in total). This sample size will also enable us to show that cryotherapy increases the cure rate from 85% to 97% (i.e. a 12% increased cure) for a similar power and significance level.

9.2 Recruitment

It is expected that five centres will recruit 3 patients per month, over a recruitment period of 18 months, giving a total of 270 participants. Northampton and Eastbourne Podiatry schools have already agreed to participate in the trial and we have approached Glasgow and Huddersfield Podiatry Schools. We will recruit other podiatry clinics by:

- Contacting the Heads of the remaining Podiatry Schools
- Networking using the Podiatry Research Forum
- Advertising in “Podiatry Now” for new centres
- Running workshops at the Podiatry Conference

The following sites have agreed to recruit participants: Huddersfield Podiatry School, Brownlow Practice Liverpool, Glasgow Podiatry School/Southern General Hospital, Springfield Surgery Bradford, Islington PCT Dr Mittal Balham London Sheffield PCT, Dr

Arthur at Claughton Medical Centre (Birkenhead, Wirral), Dr Ghori at Woodplumpton Road Surgery (Fulwood, Preston) and Dr Rajap at Arlington Road Surgery (Eastbourne).

10 STATISTICAL ANALYSIS

10.1 Primary analysis

There will be a single principal analysis at the end of the study using 5% two sided significance tests. We will use 'intention to treat' analysis. All patients will be included in their initially randomised groups whether or not they received their allocated treatment. The primary outcome is complete clearance of all verrucae at 12 weeks. The two treatment groups will be compared using simple proportions of cure or not cured using the Chi squared test. The analysis will be conducted blind to group.

10.2 Secondary analysis

As in the primary analysis, all secondary analysis will be by 'intention to treat'. For these secondary outcomes stricter statistical levels of significance will be adopted (i.e. $p = 0.01$) to reduce the chance of type I error. All analysis will be conducted blind to group.

Data on baseline demographics such as gender, age, type and duration of verrucae, previous treatments will be summarised and descriptive summary statistics provided. For variables with continuous measures we will report the mean and standard deviation, for categorical data we will report numbers and percent.

The primary analysis will be repeated, but controlling for age, whether or not the wart has been previously treated and type of wart. Should numbers be sufficient, in order to examine whether mosaic warts respond less well to treatment than simple warts, the primary analysis will be repeated, but the type of wart mosaic/simple will be included as a covariate and also an interaction term wart type*treatment will be included.[3]

Survival analysis of patient self-reported time to clearance of verrucae, censoring for loss to follow up, will be tested for using Cox regression adjusting for relevant co-variates to be defined before the analysis.

As patients and practitioner are not blinded to treatment, we will carryout a second, sub group analysis, assessing the influence of participant's treatment preference on treatment outcomes and the results of the cost effectiveness analysis.

Data on side effects of and pain intensity during and after treatment, use of painkillers, restrictions to lifestyle due to having a verruca, treatment details, patient satisfaction with treatment, number of warts, will be summarised and descriptive summary statistics provided. For variables with continuous measures we will report the mean and standard deviation, for categorical data we will report numbers and percent.

The number of patients discontinuing treatment prematurely for any reason will be summarised by treatment group and by reasons for discontinuation.

The recurrence/clearance of verrucae at 6 months will be analysed in the same way as the primary outcome measure.

10.3 Missing data

We will try and minimise any missing data with respect to the primary outcome of verrucae clearance within 12 weeks. However if we are unable to ascertain the status of any patients then they will be treated as not having a cleared verrucae in the primary analysis. Sensitivity analyses will be performed considering missing primary outcome data as positive or negative in the different treatment groups. Any missing baseline data will be imputed using appropriate methods before being used in any adjusted analyses.

The incidence of all suspected adverse treatment reactions will be summarised by treatment group.

10.4 Economic analysis

We will undertake a cost effectiveness analysis of the treatments. The costs of the two approaches will be collected as part of the study. Costs will be collected by using a patient questionnaire and from clinic records of attendances. For instance we will record the number of attendances to the health care professional both groups have (excluding the final

attendance as this a research review). We will then calculate an incremental cost per cured patient at 12 weeks.

The primary economic evaluation will be a cost effectiveness analysis of the trial treatments. The cost of resource use will be calculated for each trial participant using data collected (as described in section 7.2). Staff costs will be calculated using standard NHS costs *(Netten A Dennett J, Knight J. Unit costs of Health and Social Care. Caterbury: PSSRU, University of Kent at Canterbury, 2005*. Topical treatments will be costed using the BNF (*British National Formulary. Number 52 and* manufacture's costs where required. Patient outcome will be measured as verrucae-free days.

The incremental mean difference in costs between the two trial arms and incremental difference in patient outcome will be calculated. There are four potential scenarios:

1. Cryotherapy is less costly than salicylic acid treatment and leads to better patient outcomes
2. Cryotherapy is more costly than salicylic acid and has worse outcomes
3. Cryotherapy is more costly then salicylic acid but has better (worse) patient outcomes
4. Cryotherapy is less costly than salicylic acid treatment and leads to worse patient outcomes

If we are faced with situation 1 or 2 one treatment clearly dominates the other. That is there is a clear choice about the treatment that is cost-effective. However, if we are faced situation 3 we must weight up the potential cost implications versus patient benefit to make a decision regarding cost effectiveness. We will do this by relating the incremental mean costs between the two trial arm to the incremental mean outcome as a ratio, the incremental cost effectiveness ratio (ICER). The ICER represents the additional cost per additional verruca free day. A treatment strategy can then be considered cost-effective if the decision maker's willingness to pay for an additional verruca-free day is equal to, or greater, than the ICER Uncertainty regarding the cost effectiveness analysis will be assessed using cost effectiveness acceptability curves.

10.5 Monitoring of safety

Data presented to the DMEC will be blind to group allocation at 6 monthly intervals once recruitment has started. The number and type of adverse reaction/event will be reported and compared between the two groups.

11.0 OTHER CONSIDERATIONS

A Trial Steering Committee (TSC) will be set up to oversee the conduct of the trial. This will include an independent chair and at least two other independent members, along with the lead investigator and the other study collaborators. They will meet twice a year.

An independent Data Monitoring and Ethics Committee (DMEC) will be set up and will comprise of an independent statistician and podiatrist. The role of the DMEC is to immediately see all serious adverse events thought to be treatment related and look at outcome data at six monthly intervals.

12 PROJECT TIMETABLE

1st September 2006:	Apply for ethics, research and development (R & D) and MHRA approval for all sites as required. Approach other podiatry schools to take part in the trial, apply for ethics and R & D as appropriate.
October 2006 to Sept 2009	Start patient recruitment at Northampton, Eastbourne and new sites as soon as protocol approval/ethics/ R & D approval are received Approach GP practices to refer patients to the podiatry schools and advertise for participants eg at GP surgeries, swimming pools and local secondary schools.
March 2010	Final (6 month) follow up questionnaire sent to last participant.
April 2010 to June 2010	Data cleaning, statistical analysis and writing up study findings. Final report.
July 2010	Apply to ethics for approval of letter to be sent to trial participants informing them of the study's results. Send out results of study once approval has been received.

13 STUDY ORGANISATIONAL STRUCTURE

13.1 The York Trials Support Unit (TSU) and trial co-ordination

The York Trials Support Unit will run the trial, monitor and verify the data and analyse the results. A data coordinator, statistician, data-processing clerk and database programmer for the project will be based in the TSU.

14 PUBLICATION POLICY

The trial main trial will form the basis of an academic paper in a peer-reviewed journal on its completion. The trial team will also ensure that the results are published in a professional journal in order to ensure access by podiatrists and other health care professionals. The results of the study will be submitted for consideration at the Podiatry Conference.

Dr Mike Curran and Dr Farina Hashmi are members of the Podiatric Research Forum and they will ensure that the results of the trial are disseminated amongst health care professionals.

Participants will receive a summary of the study's findings after obtaining ethical and R & D approval.

REFERENCES

[1] McCormick A, Fleming D, Charlton J, Morbidity Statistics from General Practice Fourth National Study 1991-1992 Office of Population Censuses and Surveys Series MB5 No 3. London HMSO

[2] Gibbs S, Harvey I, Sterling JC, Stark R. Local treatments for cutaneous warts. *British Medical Journal*2002;325:461.

[3] Pocock SJ. Clinical Trials A practical approach.