PATCH
Prophylactic Antibiotics for the Treatment of Cellulitis at Home

UK Dermatology Clinical Trials Network

Randomised controlled trials to investigate whether prophylactic antibiotics can prevent further episodes of cellulitis (erysipelas) of the leg (PATCH I & PATCH II)

This protocol describes two closely related trials looking at the impact of 6 and 12 months of prophylaxis on subsequent episodes of cellulitis of the leg

PROTOCOL

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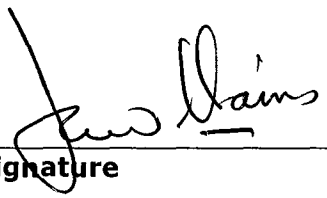

Signature

2/11/10
Date

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Site
Address 1
Address 2
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Postcode

I confirm that I agree to conduct the study in accordance with the protocol.

Principal Investigator _____ _____

Signature Date

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Title

LIST OF DEFINITIONS AND ABBREVIATIONS

Definitions

Recurrent cellulitis	Two or more documented cases of cellulitis.
Index episode	The episode of cellulitis just prior to, or at the time of entering the study.
Previous episode	Episode of cellulitis that has occurred prior to the index episode.
Repeat episode	Any episode of cellulitis (ipsi- or contra-lateral) which occurs whilst enrolled in the study, during either the treatment phase or follow-up phase.

Note: Definitions outlined above refer specifically to cellulitis of the leg.

Adverse event	Any untoward medical occurrence in a study participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse reaction	Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that subject.
Serious adverse event	An adverse event, adverse reaction or unexpected adverse reaction respectively that: (a) results in death; (b) is life-threatening; (c) requires hospitalisation or prolongation of existing hospitalisation; (d) results in persistent or significant disability or incapacity.
Suspected unexpected serious adverse reaction	A suspected unexpected serious adverse reaction.

Abbreviations

AE	adverse event
AR	adverse reaction
ASOT	anti-streptolysin O titre
bd	twice daily
CC	co-ordinating centre
CRF	case report form
CTA	clinical trials authorisation
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DVT	deep vein thrombosis
EQ-5D	EuroQol questionnaire
GCP	Good clinical practice
IE	index episode
ITT	intention-to-treat
LREC	local Research Ethics Committee
MHRA	Medicines and Healthcare products Regulatory Agency
MRSA	methicillin-resistant staphylococcus aureus
PATCH	Prophylactic Antibiotics for the Treatment of Cellulitis at Home
PI	principal investigator
RCT	randomised controlled trial
REC	Research Ethics Committee
R&D	Research & Development
SAE	serious adverse event
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
UK DCTN	UK Dermatology Clinical Trials Network

ABSTRACT

Title: PATCH (Prophylactic Antibiotics for the Treatment of Cellulitis at Home)

Objective

To assess whether a period of prophylactic penicillin after an episode of cellulitis of the leg reduces the risk of repeat episodes. This protocol describes two related studies in which participants are randomised to receive either 12 months of prophylaxis (PATCH I) or 6 months of prophylaxis (PATCH II). The PATCH I study will recruit only patients with recurrent disease and the PATCH II study will recruit patients with a first episode of cellulitis of the leg, as well as patients with recurrent disease.

Relevance of study

Cellulitis of the lower leg is an acute, painful and potentially serious infection of the skin and subcutaneous tissue. It is very common and currently accounts for 2-3% of hospital admissions[1]. The average length of in-patient stay is 9 days and 25-50% of treated patients suffer further episodes, with other associated morbidity, such as oedema and ulceration[1,2]. A reduction in the recurrence of cellulitis could have a huge impact both in terms of patient morbidity and NHS costs.

Setting

Participants will be recruited from secondary care in up to 40 centres throughout the UK and Ireland. Recruiting hospitals will be a mixture of both teaching and District General Hospitals. If recruitment should prove difficult, patients may also be identified in primary care. It is expected that 260 patients will be recruited into PATCH I and 400 patients into PATCH II.

Participants

Patients will be recruited if they have received antibiotic treatment for cellulitis of the leg within the previous 6 months.

Study design

Double-blind, placebo-controlled trials.

Interventions

Low-dose penicillin (250mg, bd) will be compared with placebo.

Data collection

Follow-up will be assessed through questionnaires, home diaries, telephone support and emergency appointments with the recruiting dermatologist. Follow-up will be continued for up to 3 years after the initial episode.

Outcomes

Identical outcome measures are to be used for both trials. The primary outcome is time to next episode of cellulitis. Secondary outcomes include:

i) the proportion of participants with repeat episodes of cellulitis;

ii) number of repeat episodes of cellulitis;

iii) proportion of participants with oedema and/or ulceration;

iv) number of nights spent in hospital for the treatment of cellulitis;

v) number of adverse drug reactions;

vi) cost-effectiveness;

vii) predictors of response (multiple regression model).

1 SUMMARY

This protocol describes two related clinical trials (PATCH I & PATCH II) that look at the impact of low-dose penicillin as prophylaxis against further episodes of cellulitis of the leg.

PATCH I: A double-blind, parallel group, randomised controlled trial comparing ***12 months*** of penicillin with placebo, in patients with ***at least 2 previous episodes*** of cellulitis of the leg.

PATCH II: A double-blind, parallel group, randomised controlled trial comparing ***6 months*** of penicillin with placebo, in patients who have received treatment for cellulitis of the leg (***both first episode and recurrent cases***).

The studies have been designed to be as similar as possible in all respects in order to facilitate comparison of data arising from the two studies. To this end, identical procedures will be followed in relation to data collection, pharmacovigilance and trial management. Outcomes will be recorded at the same time points and using the same procedures. Recruitment into the trials is to be staggered. PATCH I will begin recruiting patients in April 2006 and PATCH II will begin recruiting in November 2006. This extends the possible recruitment period for both studies and means that recruitment strategies can be refined in the light of experience.

2 PURPOSE

The studies described have been designed to address the following questions:

(1) Does a period of prophylactic antibiotic treatment after an episode of cellulitis of the leg reduce the risk of further attacks?

(2) If so:
   a) Which patients are most likely to benefit from prophylaxis?
   b) What are the cost implications for the NHS?

3 INTRODUCTION

3.1 Background

Cellulitis of the leg is an acute, painful and potentially serious infection of the skin and subcutaneous tissue. It is very common and currently accounts for 2-3% of hospital admissions[1]. The average length of in-patient stay is 9 days (Hospital Episode Statistics, Department of Health, 2002-2003) and 25-50% of treated patients suffer further episodes and other morbidity, such as oedema and ulceration[1,2].

Cellulitis of the lower leg is usually due to streptococcal infection that has entered into the body via a relatively subtle portal, such as toeweb fissures[1]. Penicillin is the most useful of the commonly used oral antibiotics against streptococci, although other agents such as flucloxacillin are often used if staphylococcal infection is a clinical possibility.

There are numerous risk factors for cellulitis of the lower leg, including previous episode(s) of cellulitis; leg oedema (especially lymphoedema); toeweb maceration (often caused by tinea pedis); obesity and diabetes[2-4]. A significant number of patients have recurrent episodes, at least in part due to the above risk factors. Recurrent disease is one the biggest problems for people with cellulitis[1]. The mechanisms of recurrent disease are uncertain and may be multifactorial - failure fully to eradicate streptococci (perhaps from damaged lymphatics) may be important[5].

Existing evidence for the use of prophylactic antibiotics to prevent further episodes is very limited. Two small randomised controlled trials (RCTs) hint at possible benefit, but these studies are very small (16 and 40 participants respectively)[6, 7]. Despite this, many physicians routinely use prophylactic antibiotics for recurrent cellulitis, although as a recent Drugs and Therapeutics review highlighted[8], opinions on the value of such practice is firmly divided.

The recently published CREST Guidelines on the Management of Cellulitis in Adults[9] recommend antibiotic prophylaxis for 1-2 years in patients with predisposing conditions who have had a least two episodes of cellulitis at the same site. The CREST Management of Cellulitis Sub-Group aims to increase awareness within both primary and secondary care of the need to improve the diagnosis and management of cellulitis, and recommend the establishment in each Trust of a champion who will promote implementation of recommended cellulitis management as outlined.

3.2 Rationale for trial

Our trial was identified as a priority topic for the UK Dermatology Clinical Trials Network (UK DCTN) because: i) it answers an important question for patients and physicians; ii)

it has significant cost implications for the NHS; and iii) it is feasible within the structure of the Network. A recent survey of the membership revealed considerable variation in the use of prophylactic antibiotics amongst dermatologists for the treatment of cellulitis. Twenty-one (29%) never used prophylaxis and 9 (12%) usually or always used prophylaxis. The majority (59%) used prophylaxis for recurrent cases or if lymphoedema was present. This variation in practice reflects the poor evidence-base for the treatment of cellulitis.

Results of an 8-month pilot study, funded by the British Skin Foundation, have been used to inform the design of the trial by helping to identify appropriate recruitment strategies, identify areas of concern to patients, and to establish the most appropriate follow-up period. This pilot study also gave principal investigators valuable training in the conduct and management of a trial run through the UK Dermatology Clinical Trials Network.

3.3 Study drug

The study drug for the treatment group is penicillin (phenoxymethylpenicillin). See Appendix 2 for Summary of Product Characteristics.

4 PLAN OF INVESTIGATION

4.1 Hypotheses

- Penicillin given prophylactically after an episode of cellulitis of the leg prevents further attacks of cellulitis.
- The protective effects of prophylactic antibiotics continue to be seen once the prophylaxis is withdrawn.

4.2 Objectives

4.2.1 Primary objective

PATCH I: To determine whether 12 months of prophylaxis with penicillin is effective in reducing repeat episodes of cellulitis in patients with ***recurrent*** (two or more documented cases) cellulitis of the leg.

PATCH II: To determine whether 6 months of prophylaxis with penicillin is effective in reducing repeat episodes of cellulitis in patients who have had cellulitis of the leg (***first or multiple*** episodes).

4.2.2 Secondary objectives (PATCH I & PATCH II)

(1) To determine whether protective benefits are observed only whilst treatment is maintained, or if benefits can continue in the longer term.

(2) To determine which baseline factors best predict treatment success.

(3) To assess whether prophylactic penicillin for cellulitis results in cost savings for the NHS.

(4) To evaluate whether there are any specific safety issues with regard to using Penicillin in this setting.

(5) To assess the impact of cellulitis on health-related quality of life.

4.3 Trial design

This protocol describes two pragmatic, double-blind, randomised controlled trials (RCTs) that compare penicillin with placebo for the prevention of further episodes of cellulitis.

PATCH I: A double-blind, parallel group, randomised controlled trial comparing ***12 months*** of penicillin with placebo, in patients with ***at least 2 previous episodes*** of cellulitis of the leg.

PATCH II: A double-blind, parallel group, randomised controlled trial comparing ***6 months*** of penicillin with placebo, in patients who have received treatment for cellulitis of the leg (***both first episode and recurrent cases***).

Recruitment into the 2 trials is staggered, with participants being entered into PATCH I as of April 2006 and into PATCH II as of November 2006. Participants are randomised to treatment groups once treatment of the initial acute episode is complete. Long-term follow-up of up to 30 months after the treatment phase is assessed through daily diaries, telephone support and emergency appointments with the recruiting dermatologist. Participants are enrolled for a minimum of 2 years and up to 3 years in total. The study is to be conducted in accordance with ICH Good Clinical Practice and the EU Clinical Trial Directive.

It is anticipated that 260 patients will be recruited into PATCH I and 400 patients will be recruited into PATCH II.

4.4 Setting

These trials are co-ordinated through the UK Dermatology Clinical Trials Network (UK DCTN), which is a collaborative network of dermatologists, dermatology nurses, health

services researchers and patients throughout the UK and Southern Ireland. Recruitment into the trials is taking place in up to 40 teaching and district general hospitals, with an option to recruit in the community, should recruitment in secondary care prove difficult. On the whole, centres will recruit patients into ***either*** PATCH I ***or*** PATCH II in order to minimise confusion and error in data recording. However, those centres that are recruiting into PATCH I will be asked to enter patients with first episode cellulitis into PATCH II as these patients will not be eligible to enter the PATCH I trial.

4.5 Selection of participants

4.5.1 Inclusion criteria

Patients will be identified by a participating UK Dermatology Clinical Trials Network clinician or dermatology nurse working at the recruiting site. Additionally patients identified in the primary care setting will be directed to a member of the study team in secondary care. Patients will be identified either at presentation or retrospectively via discharge coding, searching general practice databases, writing to patients and through adverts in relevant publications and institutions. They will be selected on fulfilment of the following criteria:

4.5.1.1 PATCH I

(1) Diagnosis of cellulitis of either leg (index episode) (see Appendix 1 for the definition of cellulitis to be used); AND

(2) history of at least one previous episode of cellulitis of either leg within the three years prior to the index episode.

4.5.1.2 PATCH II

(1) Diagnosis of cellulitis of either leg (index episode) (see Appendix 1 for the definition of cellulitis to be used).

4.5.2 Exclusion criteria

Any doubt about the certainty of the diagnosis of either the index episode or the previous episode (if applicable), will be grounds for exclusion. Additionally, patients with any of the following will be excluded:

(1) Taken antibiotic prophylaxis (defined as more than 3 months usage) for the prevention of cellulitis within 6 months prior to index episode.

(2) A time lapse of longer than 6 months since the start of treatment for the index episode to the date of the baseline visit.

(3) Known allergy to penicillin. Prospective participants will be questioned as to the nature of their previous allergic reaction in order to assess whether it was a true allergic response or simply an intolerance to the antibiotic. This questioning will address the following points:

i) whether the patient experienced a rash;

ii) when the reaction occurred in relation to administration of the drug;

iii) which type of penicillin they had.

Should the clinician deem that the reaction was intolerance rather than an allergic reaction, the clinician will discuss this issue further with the patient. The final decision as to whether to take part in the trial will rest with the patient.

(4) Preceding leg ulceration, surgery or penetrating trauma, as these cases are more likely to be caused by staphylococcal infection. (NB: this does not exclude patients with toeweb maceration/tinea pedis or other minor/blunt wounds).

(5) Treating physician or principal investigator unwilling to randomise patient. This includes, but is not limited to:

i) the treating physician and/or patient feels that prophylactic antibiotics are not in the patient's best interests and therefore entry to this study would be inappropriate.

ii) the treating physician and/or patient feels it would not be ethical or appropriate for the patient to receive placebo and so they are not willing/able to accept randomisation

ii) concomitant medication that would mean that long-term penicillin is inappropriate;

iii) diagnostic uncertainty;

iv) gastrointestinal disease causing persistent diarrhoea or vomiting severe enough to affect the absorption of the phenoxymethylpenicillin.

v) allergic diathesis or severe bronchial asthma severe enough to preclude the use of phenoxymethylpenicillin.

vi) confounding concurrent disease (e.g. DVT).

(6) Aged less than 16 years.

(7) Unable to give informed consent.

(8) Already taking part in a research study.

If a patient is discharged from hospital with prophylactic antibiotics but has agreed to

take part in the study, the principal investigator will discuss the matter with the treating physician. If both physician and patient are willing for the patient to be randomised, then enrolment will take place. If either the patient or the treating physician would prefer to continue with confirmed prophylaxis, the patient will be not be enrolled. Ideally participants will have access to a telephone to offer support however they will not be excluded if they do not.

4.5.3 Baseline record

If the patient is seen by the recruiting physician ***during the index episode***, s/he will record at baseline which of the following defining features are present:

(1) Local warmth and tenderness or acute pain (or history of).

(2) Unilateral erythema, or asymmetrical erythema with the more severe side having a temporal relationship to symptoms.

(3) Unilateral oedema.

(4) History of fever.

(5) Malaise at or just prior to current episode.

(6) Blistering/ulceration subsequent to onset of cellulitis.

(7) Exclusion of DVT, if clinically indicated.

(8) Take a blood sample to determine whether ASOT is raised 7-10 days later and record any other diagnostic blood tests taken as part of normal care.

4.5.4 Validation of diagnosis

If the patient is not seen by the clinician during the index episode but identified retrospectively, then validation of the diagnosis will be sought from the medical case notes in combination with patient discussion. Features 1 to 3 of the baseline record must have been present for the diagnosis to be validated.

4.6 Recruitment

4.6.1 Strategies

Patients with cellulitis of the leg will be identified by the principal investigator (or a designated clinician or nurse working alongside the principal investigator) at each site in secondary care. Other recruitment strategies may also be used in primary care.

(1) Suitable patients will be approached whilst at the hospital and given information

about the trial. If they agree to participate, the treating physician will be informed of this fact but will be asked not to alter his/her treatment plan for that patient.

(2) Patients will be identified after discharge via clinical data capture systems. They will be invited to attend an appointment with the recruiting physician/nurse to discuss whether they would like to participate if they have recently had an episode of cellulitis. If a longer time has elapsed since their last episode, they will be invited to contact the recruiting physician/nurse if they have another episode. This recruitment strategy will be piloted at Nottingham before full recruitment commences in order to assess the feasibility and response.

(3) Patients will be identified in the primary care setting where appropriate approvals have been sought. Posters will be displayed in waiting areas with associated information sheets enabling interested patients to contact either the local investigator in secondary care or the PATCH trial manager. The PATCH trial manager, if contacted, will provide information and local contact information where necessary. Where possible primary care institutions will mail out letters with contact details and prepaid envelopes to patients identified from a surgery database with a history of cellulitis of the leg. Advertisements in relevant publications may also be utilised.

See Appendix 3 for detailed description of recruitment strategies.

4.6.2 Timescale

Recruitment will take place over a period of 12-24 months, with the aim of recruiting 260 participants into PATCH I and 400 participants into PATCH II (see Table 1). This equates to a recruitment rate of 1-2 patients per centre per month if 30 centres are involved. However, all recruiting centres will be asked to commit from the outset to recruiting at least 3 patients per month in order to ensure recruitment success.

Recruitment rates will be reviewed regularly in order to assess the impact of the various recruitment strategies and number of effective recruitment centres. Should recruitment be slower than expected, recruitment may continue for a further 3-4 months, or until adequate numbers have been achieved for the long-term follow-up study (depending on the availability of funds).

Table 1: Project timescales

Period start date→	Oct 05	Apr 06	Oct 06	Apr 07	Oct 07	Apr 08	Oct 08	Apr 09	Oct 09	April 10
	0-6 mths	6-12 mths	12-18 mths	18-24 mths	24-30 mths	30-36 mths	36–42 mths	42–48 mths	48-54 mths	54-60 mths
Regulatory approvals										
Site identification/training of principal investigators										
Finalising documentation										
PATCH I										
Recruitment										
Treatment phase (12 months)										
Follow-up phase (non-intervention – 12 to 18 months)										
Analysis and write-up										
PATCH II										
Recruitment										
Treatment phase (6 months)										
Follow-up phase (non-intervention – 18 to 30 months)										
Analysis and write-up										

The initial 6-month set-up phase has been conducted by UK DCTN staff in order to complete the research within the time-frames of the studies funded by Action Medical Research and the BUPA Foundation.

4.6.3 Revised Timescale

Recruitment will take place over a period of 12-42 months, with the aim of recruiting 260 participants into PATCH I and 400 participants into PATCH II (see Table 2).

Recruitment rates will be reviewed regularly in order to assess the impact of the various recruitment strategies and number of effective recruitment centres. Should recruitment be slower than expected, recruitment may continue for a further 3-6 months, or until adequate numbers have been achieved for the long-term follow-up study (depending on the availability of funds).

Table 2: Revised project timescales

Period start date→	Jan 06	Jul 06	Jan 07	Jul 07	Jan 08	Jul 08	Jan 09	Jul 09	Jan 10	Jul 10	Jan 11	Jul 11
Overall timing	0-6 mths	6-12 mths	12-18 mths	18-24 mths	24-30 mths	30-36 mths	36–42 mths	42–48 mths	48-54 mths	54-60 mths	60-66 mths	66-72 mths
Regulatory approvals												
Site identification/training of principal investigators												
Finalising documentation												
PATCH I		0-6 mths	6-12 mths	12-18 mths	18-24 mths	24-30 mths	30-36 mths	36-42 mths	42–48 mths	48-54 mths	54-60 mths	66-72 mths
Recruitment												
Treatment phase (12 months)												
Follow-up phase non-intervention – 12 to 18												
Analysis and write-up												
PATCH II		0-6 mths	6-12 mths	12-18 mths	18-24 mths	24-30 mths	30-36 mths	36–42 mths	42–48 mths	48-54 mths	54-60 mths	
Recruitment												
Treatment phase (6 months)												
Follow-up phase non-intervention – 18 to 30												
Analysis and write-up												

4.7 Randomisation

On confirmation that the index episode of cellulitis has resolved, participants will be randomised to treatment using a 3rd-party randomisation service. Randomisation will be achieved using a computer-generated list produced prior to the start of the study and held by the Clinical Trials Unit, University of Nottingham, and will be concealed from the co-ordinating centre, recruiting physicians and assessors.

For **PATCH I**, randomisation will be stratified by:

i) presence of pre-existing oedema;
ii) presence of ulcer subsequent to the cellulitis;
iii) both pre-existing oedema and subsequent ulcer; and
iv) no evidence of oedema or ulceration.

For **PATCH II**, randomisation will be stratified into two groups:

i) first episode of cellulitis; and
ii) more then one previous episode of cellulitis.

Within these groups, randomisation will be stratified, as for PATCH I, by:

i) presence of pre-existing oedema;
ii) presence of ulcer subsequent to the cellulitis;
iii) both pre-existing oedema and subsequent ulcer; and
iv) no evidence of oedema or ulceration.

All trial medications will be packaged in bottles, labelled (as per Trial Medical Label - Appendix 4) and sealed in an identical fashion.

4.7.1 Blinding

The randomisation list will be held by the Clinical Trials Unit at the Queen's Medical Centre. All members of the study team will be blind to treatment allocation and analysis will be performed prior to breaking of the randomisation code. Participants will also not be told whether they have received the active or the placebo tablets and will not be informed until the end of the follow-up period. The placebo tablets used in this study will be the same size and shape as the active penicillin, and packaged in an identical way. Because it is impossible to blind the taste of penicillin, participants will be asked to swallow the tablets whole. Any decisions requiring knowledge of the treatment allocation (eg consideration of adverse events) will be referred to the data monitoring committee (DMC). If the principal investigator or the trial manager feels that blinding has been compromised in any way, details will be logged accordingly. At the end of the study, participants will be asked to record which treatment they think they received, in order to assess the success of the blinding strategy.

4.8 Interventions

The compared treatments will be:

(1) low-dose (250 mg bd) prophylactic penicillin tablets; and

(2) placebo tablets (bd) matched to the penicillin tablets as far as possible by size, colour and taste.

PATCH I trial participants will receive the study medication for a period of 12 months and PATCH II trial participants for a period of 6 months.

A dosage of 250 mg twice daily was chosen in order to reflect current clinical practice amongst dermatologists (results of an internal survey), and because the pharmacological properties of phenoxymethylpenicillin suggest that twice daily administration is preferable to once daily.

4.9 Follow-up phase (non-intervention)

After the treatment phase, participants in the PATCH I trial will be followed for up to 24 months, and participants in the PATCH II trial will be followed for up to 30 months. The duration of follow-up will depend on date of recruitment to the trial.

4.10 End of trial (treatment phase)

For regulatory purposes the end of the trial will be defined as the date of the last treatment dose for the last patient.

4.11 Participant management and data collection

4.11.1 Informed Consent

The process for obtaining subject informed consent will be in accordance with all applicable regulatory requirements. Potential participants will be supplied with a study information leaflet and given plenty of time to read it. They will also have the opportunity to discuss the trial and ask questions before being asked to sign a consent form. The principal investigator/designees and the participant (or his or her legally authorized representative) will both sign and date the consent form, and the participant will receive a copy of the form.

4.11.2 Baseline assessment

There will be a single routine examination and collection of baseline data:

i) clinical examination;

ii) details of diagnosis;

iii) potential risk factors;

iv) demographic information;

v) quality of life (using the Dermatology Life Quality Index (DLQI and the EuroQol EQ-5D) (if seen during index episode);

vi) treatment received for index episode;

vii) treatment on discharge.

4.11.2.1 Contraceptive advice

If the patient is female and of child-bearing potential, the investigator will ascertain whether she is trying to avoid pregnancy. If so, the investigator will advise the patient not to rely on oral contraceptives, and to use an additional (barrier) method of

contraception for the first month of study treatment.

4.11.2.2 Blood tests

Most patients will have a full blood count and liver and kidney function tests when they present with the index episode of cellulitis. The results of these tests will be followed up as per normal practice.

However, if these tests were not done for any reason, they will be carried out as part of the baseline visit. Any clinically significant abnormalities will be highlighted to the patient's GP or other specialist if appropriate and followed up as per normal practice.

4.11.3 Supply of trial medication

Tablets will be packaged into bottles and labelled by St Mary's Pharmacy Unit, Cardiff under the controlled conditions required for antibiotic handling. The bottles will be dispensed by the Clinical Trials Pharmacist at Queen's Medical Centre, Nottingham. Participants will receive their treatment packs by post every three months.

4.11.4 Start of trial medication

4.11.4.1 Index episode resolved

Patients whose index episode of cellulitis has resolved when they are seen by the principal investigator/designee will be eligible for randomisation immediately. Due to the potential time lapse willingness to participate and also to ensure no recurrences have occurred will be checked again by telephone from the co-ordinating centre prior to randomisation.

4.11.4.2 Index episode not resolved

Patients who are still on treatment for the index episode when they are seen by the principal investigator/designee will be asked to post a reply-paid form (Form 1 – see Appendix 3 Recruitment) to the co-ordinating centre when their treatment has ended and they are satisfied the episode is resolved (see Appendix 3 Recruitment). A pre-study telephone call will again be made before randomisation. The participant will then be randomised and sent the first pack of study medication. A reply-paid form (Form 2 – see Appendix 3 Recruitment) will be enclosed with instructions for the participant to acknowledge receipt and confirm date of starting trial medication.

4.11.5 Participant telephone contact

Participants will be contacted by telephone prior to randomisation into the study. Due to the potential time lapse between recruitment into the study and randomisation a pre-study call will re-confirm willingness to enter the study and also ensure no recurrences have occurred since consultation. This is also an opportunity to collect/confirm any outstanding baseline data. A call will then be made approximately 10 days after starting the study medication in order to check that the trial medication has been received and is being taken correctly. During this call participants will also be asked if they are happy to repeat the DLQI and EuroQol questionnaires, which will be mailed out to them. Thereafter, telephone calls will be made every three months during the intervention phase in order to collect details of repeat episodes of cellulitis, associated morbidity, adverse events and health service resource use. Telephone follow-up will occur at six-monthly intervals during the non-intervention phase of the study. If contact has not been made after repeated telephone calls over a period of four weeks, then the GP will be contacted to ascertain the participant's health status.

In a study where there is minimal contact with the investigator, a further important aspect of the telephone calls is to offer support and reassurance to trial participants. Participants will also be sent birthday and Christmas cards by the study team; this will help to keep them engaged in the study in order to reduce the number of participants who become lost to follow-up.

The telephone calls will be conducted by the trial manager and trial administrator from the co-ordinating centre.

4.11.6 Participant diary

Participants will be issued with a diary to use as an 'aide memoire' during the telephone calls and will be asked to record study medication usage, repeat episodes of cellulitis, adverse events or symptoms.

Participants will be advised to use tear-off pages within the diary to return to the co-ordinating centre for speedy notification of repeat episodes of cellulitis.

4.12 Repeat episodes

Repeat episodes of cellulitis will be verified by the principal investigator/designee using an emergency hospital appointment, or (if this is not possible), by contact with the patient's GP. If neither is possible, then the repeat episode will be classed as self-

reported (see Definitions (page 7) for details of this classification). Results of a focus group discussion, involving 5 patients who had experienced cellulitis, suggested that patients were confident of their ability to identify further attacks, particularly when they had already experienced several episodes.

4.12.1 Confirmed repeat episodes

Guidance issued to participants will advise them to try and make an appointment with the principal investigator/designee for treatment, or if this is not possible, then to seek medical help as required, using normal health care facilities.

If the principal investigator/designee is not able to see the participant during the repeat episode, as soon as s/he is aware of it, s/he will contact the patient to ask:

i) which medical professional (if any) they saw;

ii) where they saw them;

iii) what symptoms they had;

iv) whether or not the diagnosis of cellulitis was confirmed;

v) what treatment they were given.

The principal investigator/designee will then seek confirmation of the diagnosis from the patient's notes and record any other diagnostic blood tests (including ASO titre) taken as part of normal care . If the participant was seen by the GP, then the principal investigator/designee or the Clinical Trial Manager will seek confirmation of the diagnosis from the practice manager.

If confirmation of the diagnosis of cellulitis can be made then the episode will be classed as a confirmed episode.

4.12.2 Self-diagnosed repeat episodes

If the patient reports a repeat episodes which has been treated with antibiotics, but it is not possible to confirm this from medical notes, the repeat episode will be classed as a self-diagnosed episode.

The participant management schedule is summarised in Table 3.

Table 3: Summary of participant schedule

SCREENING PHASE			**INTERVENTION PHASE**						
	[1]Done by PI	When IE resolved	PATCH I and II				PATCH I only		All repeat episodes
			[2]Day 0	Day 10	3 mths	6 mths	9 mths	12 mths	
Screening	X								
Informed consent	X								
Clinical examination	X								
Baseline assessment	X								
DLQI[3]	X			X					X
EuroQol EQ-5D[3]	X			X					X
Randomisation		X							
Start study medication			X						
Telephone call (for support and to collect details of adverse events and health service resource use)				X	X	X	X	X	X
Urgent appointment with principal investigator									X

[1] Either during index episode (IE) or at appointment

[2] Day 0 must be no later than 12 weeks after the start of index episode treatment

[3] May on occasionally be sent by co-ordinating centre

	NON-INTERVENTION FOLLOW-UP PHASE			
	PATCH II only	PATCH I and II	PATCH I only	All repeat episodes
	12 mths	18 mths	24 mths	
Telephone call (for support and to collect details of adverse events and health service resource use)	X	X	X	X
Urgent appointment with principal investigator				X

4.13 Stopping rules/withdrawals

(1) Any patient who experiences an adverse reaction to the study medication or who wishes to stop taking the medication for any reason will be free to cease trial medication at any time. This will not require a breaking of the randomisation code and participants will continue to be followed up in the usual way. However, participants are free to withdraw completely from the study if they wish.

(2) Should a participant have a repeat episode of cellulitis that requires treatment, they will be instructed to stop taking the trial medication and to take the treatment prescribed for the new episode of cellulitis as instructed. Once treatment of the repeat episode is complete, they will be encouraged to go back on the trial medications as before. The treating physician will not need to break the randomisation code in this instance. Any break in the study drug during treatment for a repeat episode should be recorded in the CRF.

(3) If it is decided that a patient should have long-term antibiotics on the basis of clinical need for preventing cellulitis, then the study medication will be stopped and the participant will be withdrawn from the study. Patients will be followed up in the usual way where possible.

4.14 Compliance/Concordance

Participants will be asked to record their study medication compliance in their diary. In addition, they will be asked about compliance during the telephone contacts.

5 OUTCOME MEASURES

5.1 Primary outcome measure

(1) Time to next episode of cellulitis

The next episode is defined as the next episode of cellulitis (in either leg) that has been reported by the participant, and confirmed by a medical practitioner (GP or physician working in secondary care). The episode will be considered as starting on the first day of symptoms reported by the participant. Episodes that are reported by the participant and result in antibiotic treatment but are not confirmed by a medical professional will be documented as self-reported cases.

5.2 Secondary outcome measures

(1) Proportion of participants with repeat episodes of cellulitis in the active treatment arm compared with the placebo treatment arm at the end of the treatment phase, and at the end of the non-intervention follow-up phase.

(2) The number of repeat episodes of cellulitis.

(3) Proportion of participants with oedema and/or ulceration in the active treatment arm compared with the placebo treatment arm at the end of the treatment phase, and at the end of the non-intervention follow-up phase.

(4) Number of nights in hospital for the treatment of repeat episodes of cellulitis.

(5) Number of adverse drug reactions reported in each treatment arm.

(6) Cost-effectiveness – including GP consultations, prescriptions for antibiotics and days in hospital.

(7) Predictors of response multiple regression model to explore the impact of known risk factors in predicting the efficacy of prophylaxis. Separate models will be developed for ipsi-lateral and contra-lateral episodes in relation to different risk factors.

In addition, the impact of cellulitis on health-related quality of life will be assessed through a comparison of questionnaire scores during the index episode (if the participant is seen at this time), compared to those carried out once the cellulitis has resolved or at repeat episodes.

6 ANALYSIS

6.1 Analysis plan

A detailed analysis plan will be prepared prior to conducting the analysis and will be conducted according to the principles of intention-to-treat and will be based on the MRC Clinical Trials Unit standard operating procedure for trial data analysis.

6.2 Primary outcome

Time to recurrence will be assessed using survival analysis. Patients who have limited follow-up data will be included in the analysis, but will be censored accordingly.

6.3 Secondary outcomes

Secondary outcomes 1 to 5 will be analysed using a chi-squared analysis in the first instance. In addition, a predictors of response model will be developed using a logistic regression model, with recurrence or no-recurrence as the dependent variable.

The two studies will be compared and comment will be made with regard to any effects that might be attributable to differences in the duration of prophylaxis. It will be made clear in any such analysis that this is an indirect comparison on different populations.

6.4 Sample size

The sample size estimates tabulated below assume an ability to detect a 50% reduction in relapse rate relative to placebo. It was felt that a 50% reduction relative to placebo was needed as a minimum clinically useful gain, given the lengthy duration and possible inconvenience of long-term prophylaxis.

Previous studies have suggested a range of possible recurrence rates for patients not

receiving prophylaxis of between 20 and 50 %[1,3], depending on the population being studied and the duration of follow-up. The table below provides sample size estimates for various relapse rates, assuming 80% power and a significance level of 5%. In order to achieve 90% power, the sample estimate would need to be increased by approximately one third. All randomised participants will be included in the final analysis whether they took any study medication or not.

PATCH I

With a relapse rate in the placebo arm of 35% (relapse-free survival rate = 0.65), 260 participants will provide sufficient power to detect a 50% reduction in relapse rates compared to placebo (80% power, 20% loss to follow-up). We therefore aim to recruit 260 participants over a period of 12 months, at a rate of 20-25 per month (1-2 per centre per month).

A relapse rate in the placebo arm of 35% was chosen as a conservative estimate. Since having had a previous episode of cellulitis is an important risk factor for future episodes[2,4], it is most likely that the recurrence rate in the placebo arm will be higher (between 35 and 50%).

	PATCH I		PATCH II
Relapse-free survival rate at 2.5 years (placebo)	0.65	*0.50*	0.75
Relapse-free survival rate at 2.5 years (active)	0.825	*0.750*	0.875
N per arm	103	*62*	157
N per arm with 20% loss to follow-up	129	*78*	197
Total for study (both treatment arms)	**258**	***156***	**394**

PATCH II

It is anticipated that the relapse rate in the placebo arm will be lower for PATCH II as patients with first episode cellulitis will be included as well as though with recurrent disease. With a relapse rate of 25% (relapse-free survival rate = 0.75), 400 participants will provide sufficient power to detect a 50% reduction in relapse rate compared to placebo (80% power, 20% attrition). We therefore aim to recruit 400 participants into PATCH II over a period of 18-24 months, at a rate of 20-25 per month (1-2 per centre per month).

Results of the recent pilot study involving patients with a first episode of cellulitis, as well as those with recurrent disease, support these estimates: of the 70 cellulitis patients recruited, 32% had had a previous episode of cellulitis within the last 3 years, giving an estimated relapse-free survival rate for the placebo arm of 0.68.

6.5 Economic analysis

A cost-effectiveness analysis will be conducted alongside the RCT in order to determine the possible cost implication of the intervention from the perspective of the NHS. Six months of treatment with penicillin costs £20 (£40 for twelve months). By contrast, a single hospital admission (average = 9-10 day stay) costs approximately £2,000.

For the purposes of this study, data will be collected on the number of nights spent in hospital; the number of GP consultations; the number of courses of antibiotics prescribed for the treatment of cellulitis; and the number of related investigations.

Cost-effectiveness data will be presented for both unit resource use and total costs from the perspective of the National Health Service. The unit of effect will be future episodes of cellulitis avoided, and health utility of an avoided episode will be estimated from data collected at baseline using the EQ-5D. Data will be analysed using either conventional statistical techniques or bootstrapping methods[10] depending on the distribution of the cost data.

7 TRIAL MANAGEMENT PLAN

7.1 Trial management

The study will be managed by a trial steering group made up of the applicants; the manager of the UK DCTN (Dr Joanne Chalmers); the Clinical Trial Manager employed to co-ordinate the trial (Dr Katharine Foster); a health economist; and an independent chairperson (Dr Peter Featherstone). This group will be responsible for the day-to-day management of the study and for ensuring that all reports, amendments and adverse drug reactions are submitted in a timely fashion.

A panel of 5 service users with experience of cellulitis will also advise the group. These individuals have been identified following a recent article in LymphLine (the newsletter for the Lymphoedema Support Network).

A data monitoring committee (DMC) will be convened prior to starting the trial and will follow MRC guidelines for the conduct of the DMC. The main responsibilities of the DMC will be to oversee recruitment rates and safety issues relating to the trial. The Independent Data Monitoring Committee is chaired by Dr Robert Hills (Satistician) and also includes a consultant dermatologist and clinical trialist.

All SAEs that could potentially be related to the study intervention will be reported to the Chair of the DMC as a priority. The Chair will assess whether or not the event should be submitted as a SUSAR on behalf of the DMC.

7.2 Training of PIs and other personnel involved in the trial

A PowerPoint presentation will be provided to all participating investigators, which will summarise the main commitments and procedures involved in the trial; they will also receive a presentation outlining the results of the pilot study. This will be supplemented by an investigator manual containing relevant standard operating procedures (SOPs), case report forms (CRFs) and contact details. All principal investigators will be required to sign that they have read and understood this material. Where questions arise, these will be dealt with by the trial manager employed to manage the trial. If the local principal investigator is new to clinical research, a site visit may be necessary. In addition, all members of the UK DCTN are invited to attend regular GCP update courses.

7.3 Data management

Data will be managed centrally at the Centre of Evidence Based Dermatology and the Nottingham Clinical Trials Unit. All data will be entered onto a customised database. Validation rules and checks will be built into this database. Any inconsistencies will be investigated by the trial manager and discussed with the DMC as appropriate.

Paper data will be stored in a locked filing cabinet and electronic data will be password-protected. Contact details will be held in a separate, secure database in order to allow the researchers to contact the participants at intervals over the 3-year study. Participants will be identified in the trial database by unique reference number and initials only.

Copies of the case report forms (CRFs) and the original consent forms will be stored at the participating sites. All data will be stored in a locked drawer or filing cabinet. The local principal investigator will be responsible for ensuring that personal data are handled in accordance with the Data Protection Act.

The PIS will contain the information for the participant to know that their data will be collected and used for analysis.

7.4 Archiving

On closure of the trial, all essential documents relating to the study will be archived centrally for a minimum period of 7 years in accordance with sponsor policy the EU Clinical Trials Directive (Directive 2001/20/EC). Duplicate copies of CRFs held at the recruiting centres will be destroyed at this time.

8 ADMINISTRATIVE AND REGULATORY MATTERS

8.1 Funding

8.1.1 Source

The study is financed through grants from Action Medical Research (PATCH I) and the BUPA Foundation (PATCH II).

8.1.2 Conflict of interest

None of the study personnel have any financial interest in this proving to be a successful intervention – any benefit will be in reducing morbidity for this group of patients and an overall reduction in costs to the NHS.

8.2 Sponsor

The University of Nottingham has agreed to act as sponsor for the trials and will provide non-negligent indemnity cover for aspects relating to the study protocol. Local Trusts will be required to provide indemnity for negligent harm arising from activities performed by clinicians operating under their jurisdiction.

8.3 Authorisation certificate

A clinical trials authorisation (CTA) certificate will be obtained from the MHRA as the study falls under the remit of the EU Clinical Trials Directive 2001/20/EC. The University of Nottingham will be responsible for registering the study on the EudraCT database and ensuring that the study is conducted in accordance with Good Clinical Practice and the Research Governance Framework.

8.4 Research Ethics Committees approval

REC approval will be sought for this study prior to commencement, and site-specific assessments performed by the relevant LRECs. All local principal investigators will apply for R&D approval through their employing NHS Trust.

8.5 Risk Assessment

This is a low-risk trial with clear and easily verifiable outcomes. It is not therefore necessary to implement extensive monitoring. The main risk to the integrity of the data lies in the possible inexperience of many of the local investigators, coupled with limited local research support. These risks will be managed by the provision of training and

support for all participating physicians. In addition, many of the recruiting centres for this study are likely to be those involved in the pilot study who have gained valuable experience in this area of clinical research.

8.6 Monitoring procedures

As this has been assessed as a low-risk trial, on-site monitoring is not considered necessary. We propose to implement central monitoring, with targeted site visits as required. Where facilities allow, the R&D departments in participating Trusts will be asked to assist with on-site monitoring through their existing trial monitoring arrangements.

Original signed consent forms will be retained at each centre.

8.7 Adverse event reporting

Details of adverse reactions and events will be collected throughout the period that participants receive treatment. They will be recorded in the patient diaries and discussed during the 3-monthly telephone calls.

Penicillin has been widely used for many years and as a result the safety profile of the drug is well established. It is therefore the aim of these studies to collect detailed safety data which are relevant to the specific use of penicillin under the conditions described here.

8.7.1 Adverse reactions

Adverse reactions (ARs) relating to the use of penicillin are well documented (eg nausea, diarrhoea), although the doses used in the current study are very low and are unlikely to give rise to such reactions. Details of ARs will be collected through participant diaries and telephone calls and reported on an annual basis.

There are a number of conditions that may conceivably be related to the long-term use of penicillin and/or exposure to streptococcal infection. As a result, participants will be specifically questioned during telephone contacts and any clinic visits about the following conditions:

i) necrotising fasciitis
ii) penicillin-resistant sepsis
iii) exfoliative dermatitis
iv) toxic epidermal necrolysis
v) streptococcal toxic shock-like syndrome (STSS)

vi) renal impairment

vii) vulvo-vaginitis

Should any of these events occur, they will be reported to the DMC in an expedited fashion as soon as the co-ordinating centre is aware of them. If any of the events constitute an SAE, then they will be reported as described in section 8.7.2.

For the reasons described above, adverse events which are unrelated to penicillin will not be collected or analysed. Hospitalisation due to recurrence of cellulitis of the leg also will not be reported as a serious adverse event as this is an anticipated consequence for a percentage of participants on this study and indeed is the primary end-point.

8.7.2 Serious adverse events

Given that the population being studied is predominantly elderly, it is likely that many serious adverse events (SAEs) will occur during the study period. However, most of these SAEs will be unrelated to the trial intervention. For the reasons described above data on unrelated SAEs will not be collected or analysed.

Any SAEs that are thought to be related to the study drug (including the above list) will be reported by the principal investigator to the co-ordinating centre within 24-48 hours of discovery. However, it is likely that SAEs will be reported directly by patients to the trial manager, who will ensure that the PI is made aware of the event, if appropriate.

If an SAE is reported that is unexpected and is possibly, probably or definitely related to the study drug, the event will be reported in an expedited fashion to the Chair of the DMC, as a possible SUSAR (see section below).

8.7.3 Suspected unexpected serious adverse reactions

Any SAEs that are unexpected and thought to be related to the intervention will be referred to the principal investigator in order to clarify whether or not the event should be reported as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

Any confirmed SUSARs will be communicated to the other investigators taking part in the study.

8.7.4 Expedited reporting of SAEs and SUSARs

The trial manager is responsible for reporting SAEs and SUSARs to the MHRA (and other European competent Authorities if appropriate) in accordance with current regulations.

8.8 Publication policy

Findings from these studies will be published in the public domain by the steering group

on behalf of the UK DCTN. Conditions of authorship will be in line with the guidelines currently available for major peer-reviewed journals. This includes a substantial contribution to:

- conception and design, or analysis and interpretation of data;
- drafting the article or revising it critically for important intellectual content;
- and final approval of the version to be published.

Participation solely in the acquisition of funding or the collection of data will not justify authorship. Nevertheless, all those who help with the recruitment of trial participants will be appropriately acknowledged at the end of the paper.

Results will be published in a leading peer-reviewed journal (eg *The Lancet*) and presented at relevant academic meetings. It is anticipated that PATCH I will be published approximately twelve months in advance of PATCH II.

The trials will also be registered on the International Standard Randomised Controlled Trial Number (ISRCTN) register and the Cochrane Skin Group on-going trials register, both of which are freely available in the public domain.

Trial participants will be informed of the results of both studies once analysis is complete and articles will be placed in relevant patient support magazines (eg LymphLine).

Funding of the trials by Action Medical Research (PATCH I) and the BUPA Foundation (PATCH II) shall be acknowledged on all papers and presentations. These funding bodies shall be advised in advance of any publications arising from the project, and dissemination of findings shall be discussed with the public relations departments of the two charities as appropriate. The support of the National Co-ordinating Centre for Research Capacity Development (NCC RCD) in funding the co-ordinating centre for the UK DCTN will also be appropriately acknowledged.

APPENDIX 1

POINTS RAISED DURING PROPOSAL DEVELOPMENT AND PILOT STUDY

Many points have been raised during the development of this project. Some of the most commonly raised issues are summarised below, along with our considered responses.

Definition of cellulitis

Our preliminary definition of cellulitis was based on the definition given in the recent Drug and Therapeutics bulletin and required 'erythema, oedema and warmth accompanied by acute pain, tenderness and an associated constitutional disturbance'. Results of the pilot study suggested that inclusion criteria based on a strict checklist of current symptoms could result in the loss of up to 44% of otherwise eligible patients (ie those confirmed as having cellulitis by the recruiting dermatologist). Entry criteria have therefore been based on a confirmed diagnosis of cellulitis by a general physician, dermatologist or dermatology nurse, along with a checklist of presenting features that will be used to describe the study population.

What kind of patients should be included?

It was originally our intention to recruit all patients with cellulitis, as this provides the opportunity to look at possible predictors of response for the whole patient group, rather than just those with recurrent disease. However, recruiting only recurrent cases is a better reflection of current clinical practice, and was recommended by Action Medical Research during the funding application. This has therefore become the basis for the PATCH I trial. However, the award of a further grant, from the BUPA Foundation, has allowed us to implement our original strategy of recruiting patients with either first-episode or recurrent cellulitis into a 6-month intervention trial (PATCH II).

How long a period of prophylaxis?

The duration of prophylaxis is key to the success of this trial. A previous survey of the membership of the UK DCTN suggested that clinicians currently prescribe prophylaxis for anything from 3 months to indefinitely. For the purposes of this study, is was important that we chose a period of prophylaxis that was sufficiently lengthy to result in benefit, but was not so long as to result in poor compliance by the participants. Treatment periods of 6 or 12 months have been chosen to reflect these conflicting needs and provide a useful comparison of the two periods of treatment.

Results of the pilot study (unpublished) suggested that patients would largely be willing to take prophylactic antibiotics for a period of up to 12 months, provided that sufficient reassurances were given that the antibiotic was specific to streptococcal infection, and that they could stop the trial medication in order to receive active medication if they

suffered a further attack.

Should streptococcal causation be proven prior to enrolment in the study?

In most cases it is difficult to prove streptococcal causation by bacteriology or ASO titre. Published data suggest that this gives only a 20-25% yield[11,12]. As a result, we propose to record results of ASOT testing at 7-10 days (where performed as part of routine practice) in order to inform the predictors of response model. In addition, by excluding those with chronic wounds/leg ulcers or cellulitis confined to the area around trauma/surgical wounds, we should minimise the risk of including non-streptococcal cases.

Resistance

We are not aware that resistance to penicillin is likely to be a problem. It is our belief, and that of our microbiology advisor, that i) the risks of developing antibiotic resistance at both the patient and a population level are extremely small; and that ii) the emergence of MRSA is not associated with the use of narrow spectrum penicillin. Penicillin has been used as long-term medication for many years in other conditions such rheumatic fever, and group A streptococcus has remained susceptible to penicillin for over 60 years, without signs of developing resistance[13]. Nevertheless, part of the remit of the DMC will be to review these issues.

If patients have any concerns about resistance, the principal investigator/designee will take time to discuss the issue fully with them. In addition, the patient information leaflet will address this issue.

Patients with allergy to penicillin

The pilot study suggested that more patients than expected reported an 'allergy' to penicillin. It would not be possible to provide an alternative to penicillin within the current trial, as this would require a double dummy design. Patients reporting an allergy to penicillin will be questioned further in order to establish the exact nature of the allergic response. This will distinguish between those with a definite allergic response (who will be excluded) and those with a mild reaction to penicillin (who will be eligible for inclusion). The final decision as to whether or not to take part in the study will rest with the patient.

APPENDIX 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 Trade name

Penicillin VK tablets 250 mg

2 Qualitative and quantitative composition

Each tablet contains 250 mg phenoxymethylpenicillin (as phenoxymethylpenicillin potassium). For excipients see 6.1.

3 Pharmaceutical form

Film-coated tablet.

4 Clinical particulars

4.1 Therapeutic indications

For use in the treatment of mild to moderately severe infections caused by penicillin-sensitive organisms.

4.2 Method of administration

Each tablet should be swallowed whole with water, at least 30 minutes before food, as ingestion of phenoxymethylpenicillin with meals slightly reduces the absorption of the drug.

Dosage:

- *Adults:* The dosage is 250-500 mg every six hours
- *Elderly:* The dosage is as for adults. The dosage should be reduced if renal function is markedly impaired.
- *Prophylactic use:* The dosage is 250 mg daily for long-term prophylaxis of rheumatic fever.
- *Children:* 1-5 years 125 mg every six hours

  6-12 years 250 mg every six hours

4.3 Contra-indications

Phenoxymethylpenicillin is contra-indicated in patients with known penicillin hypersensitivity.

4.4 Special warnings and special precautions for use

Phenoxymethylpenicillin should be given with caution to patients with a history of allergy, especially to other drugs. Phenoxymethylpenicillin should also be given

cautiously to cephalosporin-sensitive patients, as there is some evidence of partial cross-allergenicity between the cephalosporins and penicillins. Patients have had severe reactions (including anaphylaxis) to both drugs. If the patient experiences an allergic reaction phenoxymethylpenicillin should be discontinued and treatment with appropriate agents initiated.

Particular caution should be exercised in prescribing phenoxymethylpenicillin to patients with an allergic diathesis or with bronchial asthma.

Oral penicillins are not indicated in patients with a gastrointestinal disease that causes persistent diarrhoea or vomiting, because absorption may be reduced.

In patients undergoing long-term phenoxymethylpenicillin treatment the complete and differential blood count, as well as the liver and kidney function, should be monitored. During long-term treatment attention should also be paid to the potential overgrowth of resistant organisms including *pseudomonas* or *candida.*

Each tablet of Penicillin VK Tablets 250 mg/Ospen Tablets 250 mg/Apsin VK 250 mg Tablets/Stabilin VK 250 mg Tablets/Veepen 250 mg Tablets and Brit-V Tablets contain 28 mg of potassium, which may be harmful to people on low potassium diets and may cause stomach upset, diarrhoea and hyperkalaemia. High doses should be used with caution in patients receiving potassium-containing drugs or potassium-sparing diuretics.

In renal impairment the safe dosage may be lower than usually recommended.

4.5 Interactions with other medicaments and other forms of interaction

As penicillins like phenoxymethylpenicillin are only active against proliferating micro-organisms, phenoxymethylpenicillin should not be combined with bacteriostatic antibiotics.

Concomitant use of uricosuric drugs (eg probenecid) reduces the excretion of phenoxymethylpenicillin, resulting in increased plasma levels.

Combined use of phenoxymethylpenicillin and oral anticoagulants (eg warfarin) may prolong prothrombin time.

Phenoxymethylpenicillin may reduce the excretion of methotrexate, causing an increased risk of toxicity.

Like other antibiotics, phenoxymethylpenicillin may reduce the effectiveness of oral contraceptives.

During treatment with phenoxymethylpenicillin non-enzymatic urinary glucose tests may be false-positive.

Neomycin reduces the absorption of phenoxymethylpenicillin.

4.6 Pregnancy and lactation

No effects have currently been shown. General caution should be exercised when prescribing to the pregnant patient.

4.7 Effects on ability to drive and use machines

There are no effects on ability to drive or to operate machinery.

4.8 Undesirable effects

Potential allergic reactions include urticaria, angioneurotic oedema, erythema multiforme, exfoliative dermatitis, fever, join pain or anaphylactic shock (which could be fatal) with collapse and anaphylactoid reactions (asthma, purpura, gastrointestinal symptoms). These are less common, and take a milder course, in oral treatment than during parenteral penicillin treatment.

Nausea, diarrhoea, vomiting, stomatitis and glossitis are sometimes seen.

Sustained severe diarrhoea should prompt suspicion of pseudomembranous colitis. As this condition may be life-threatening phenoxymethylpenicillin should be withdrawn immediately and treatment guided by bacteriologic studies.

Eosinophilia, haemolytic anaemia, leucopaenia, thrombocytopaenia and agranulocytosis are extremely rare.

As with other broad-spectrum antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms, eg candida. This may present as vulvo-vaginitis.

4.9 Overdose

A large overdose may cause nausea, vomiting and diarrhoea. Rarely major motor seizures may occur. There is no known antidote. Symptomatic and supportive therapy is recommended. Phenoxymethylpenicillin may be removed by haemodialysis.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Phenoxymethylpenicillin is a broad-spectrum antibiotic for the treatment or prophylaxis of mild to moderate infections caused by susceptible Gram-positive organisms.

5.2 Pharmacokinetic properties

Following administration by mouth absorption is usually quick, complete and rapid from the gastrointestinal tract. Peak serum concentrations of 3-6 µg per ml have been seen following dosage of 250 mg to 500 mg by mouth. The effect of food on absorption is slight and variable.

The plasma half-life of phenoxymethylpenicillin is about 30 minutes, which may increase

to four hours in renal failure. Eighty per cent is reported to be protein-bound. Phenoxymethylpenicillin is widely distributed round the body tissues and fluids and more readily penetrates inflamed tissues. It also diffuses across the placenta into foetal circulation and small amounts appear in the milk of nursing mothers.

Excretion is by tubular secretion into urine. Some metabolism occurs in the liver and several metabolites have been found, including penicilloic acid. Small excretion occurs in bile. Impaired absorption is seen in patients with celiac disease.

5.3 Pre-clinical safety data

No data of clinical relevance.

6 Pharmaceutical particulars

6.1 List of excipients

Tablet core: magnesium stearate
talc (E553b)
macrogol 6000
povidone (E1201)
maltodextrin

Tablet coating: titanium dioxide (E171)
hypromellose (E464)
talc (E553b)

6.2 Incompatibilities

There are no known incompatibilities.

6.3 Shelf life

This medical product as packaged for sale has a shelf life of five years.

6.4 Special precautions for storage

The following applies to the storage of Penicillin VK Tablets 250 mg/Ospen Tablets 250 mg/Apsin VK 250 mg Tablets/Stabilin VK 250 mg Tablets/Veepen 250 mg Tablets and Brit-V Tablets 250 mg:

- 'Do not store above 25°C'
- 'Store in the original packaging' (when packed in blisters)
- 'Keep the container tightly closed' (when packaged in securitainers)

6.5 Nature and contents of container

The 250 mg film-coated tablets are present in the following containers:

- Amber glass bottles with polyethylene twist-off closures containing 50 or 100 tablets
- Polypropylene containers with polyethylene snap-on caps containing 50, 500 or 1000 tablets
- Blister strips of 10, 14, 20, 21 or 28 tablets

6.6 Instructions for use/handling

There are no particular instructions from handling.

7 Marketing authorisation holder

Biochemie GmbH
A-6250 Kundl
Tirol
Austria

8 Marketing authorisation number

04520/0005

9 Date of first authorisation/renewal of the authorisation

26 November 1998 (latest renewal date)

10 Date of (partial) revision of the text

3 September 2001

APPENDIX 3

RECRUITMENT STRATEGIES

Results of the pilot study suggest that the most difficult aspect of this project is likely to be recruitment into the trial. This is largely because patients coming to hospital with cellulitis are not routinely seen by dermatologists and are often difficult to locate. It is anticipated that recruiting centres will select the recruitment strategy most suited to their individual Trust. Where recruitment from primary care is viable the appropriate approvals will be sought. Advertising in relevant publications and searching of relevant databases may be utilised. Funding may be provided to active recruiting centres to enable someone to dedicate time to the PATCH studies. This may be utilised to identify and recruit participants, for example, with administrative help or liaising with colleagues in other wards/departments. Additionally a token reward (for example a box of chocolates) may occasionally be offered to colleagues at PATCH centres who have worked hard or been very helpful to the study and/or study team.

Three main models of recruitment are suggested:

Model 1

Patients with cellulitis of the leg will be identified whilst in hospital by the principal investigator (or a designated clinician or nurse working alongside the principal investigator) at each site. Patients will be approached by the local investigator/designee whilst at the hospital and given information verbally about the trial and a copy of the patient information sheet. If they agree to participate, after time for consideration and an opportunity to ask questions, the treating physician will be informed of this fact but will be asked not to alter his/her treatment plan for that patient.

Each recruiting centre will employ the strategies most appropriate in their own Trust to identify these patients. These may include:

- Visiting the relevant wards (admissions/infectious diseases/dermatology etc) to identify patients from the admissions book.
- Raising awareness of the study amongst other physicians and asking for referrals (with the patient's consent for his or her details to be passed to the principal investigator).

Once a prospective participant has been identified, the route followed will be as set out in the flowchart for Model 1. Patients will be approached whilst at the hospital and given information about the trial.

Prospective participants who are discharged on short-term antibiotic treatment will be issued with a reply-paid form (Form 1) and instructed to complete and return it to the

co-ordinating centre when their treatment has ended. This form will ask the patient if their leg has returned to normal or almost normal. If the cellulitis has resolved, they will be randomised and enrolled in the trial. If the cellulitis has not resolved, they will be advised to telephone the principal investigator/designee to discuss the best course of action. Should the patient require a further course of antibiotics that results in more than the allowed 6 months of treatment for the index episode (see exclusion 2) then they will be not be enrolled into the study. Participants who are deemed eligible for recruitment will be randomised and sent the study medication with a reply-paid form (Form 2) asking them to acknowledge receipt of medication and confirm date of commencement.

Documentation

The documentation employed in the Model 1 recruitment process will be as follows:

- Patient information sheet
- Informed consent form
- Form 1 – (to be posted by prospective participant to the co-ordinating centre when their treatment has ended)
- Form 2 – (to be posted by participant to the co-ordinating centre to acknowledge receipt of study medication and confirm date of starting trial medication)
- DLQI and EuroQol EQ-5D
- Participant diary

MODEL 2

Clinical data capture systems within the Trust will be used to identify patients with a diagnosis of repeat cellulitis of the leg who have been admitted and discharged without coming to the attention of the principal investigator. Care will be taken not to approach patients who have already been screened for the study whilst in hospital. For these prospective participants, the route followed will be as set out in the flowchart for Model 2.

Documentation

The documentation employed in the Model 2 recruitment process will be as follows:

- Letter 1 to patient with enclosures:
    - Patient information sheet
    - Reply form
    - Reply-paid addressed envelope
- Letter 2 to patient giving date and time of appointment with principal investigator
- Informed consent form

- Form 1 – (to be posted by prospective participant to the co-ordinating centre when their treatment has ended)
- Form 2 – (to be posted by participant to the co-ordinating centre to acknowledge receipt of study medication and confirm date of starting trial medication)
- DLQI and EuroQol EQ-5D
- Participant diary

MODEL 3 – Primary care

For these prospective participants, the route followed will be as set out in the flowchart (Model 3) for primary care.

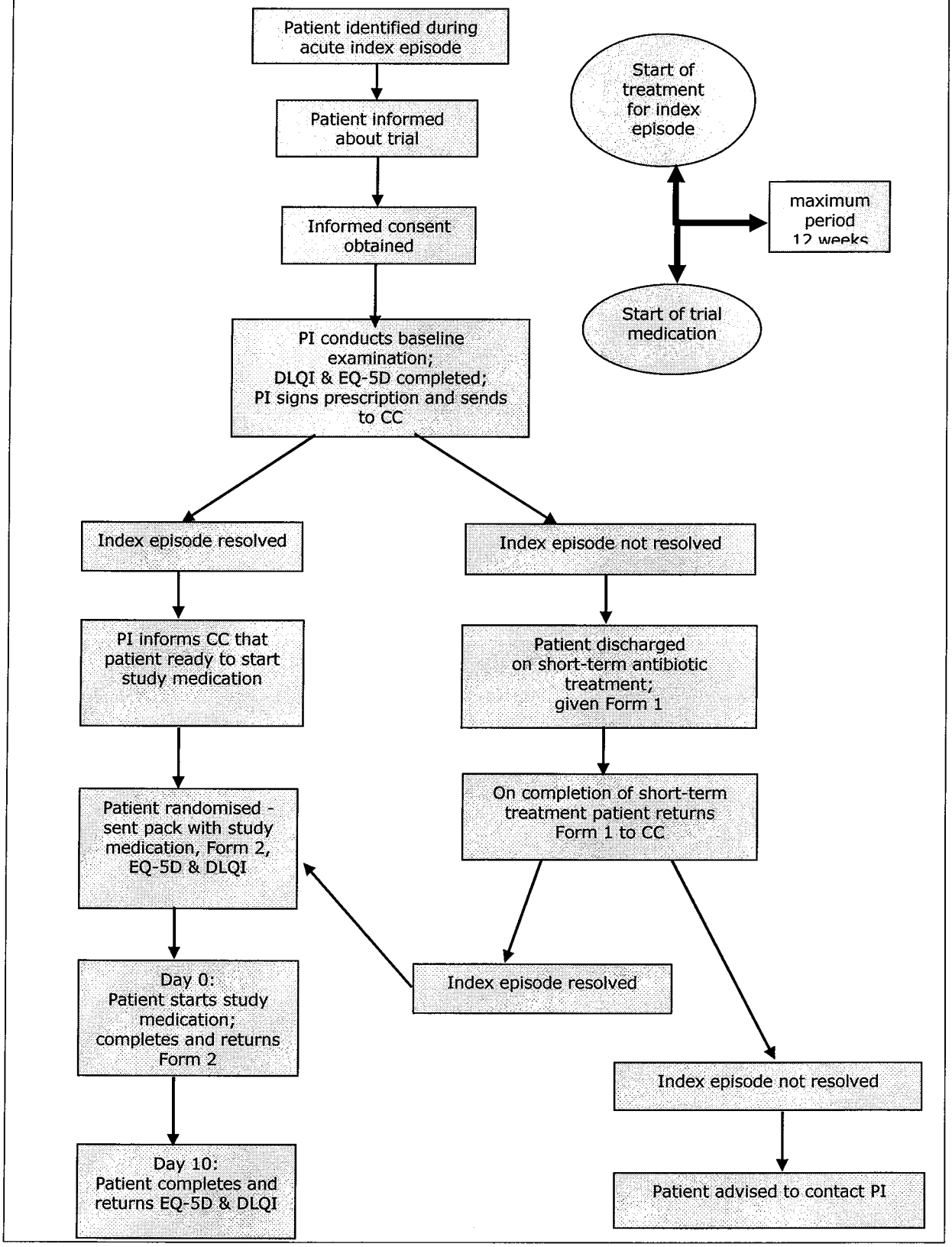
Potential participants may see a poster/advert and pick up a summary information sheet with contact details. They may then make contact with the co-ordinating centre or local investigator directly. If contact is made with the co-ordinating centre initially they will pass on the details to the local investigator. Alternatively the GP or relevant designee (such as practice manager) may search the relevant database for a diagnosis of cellulitis of the leg and mail out letters where appropriate.

Documentation

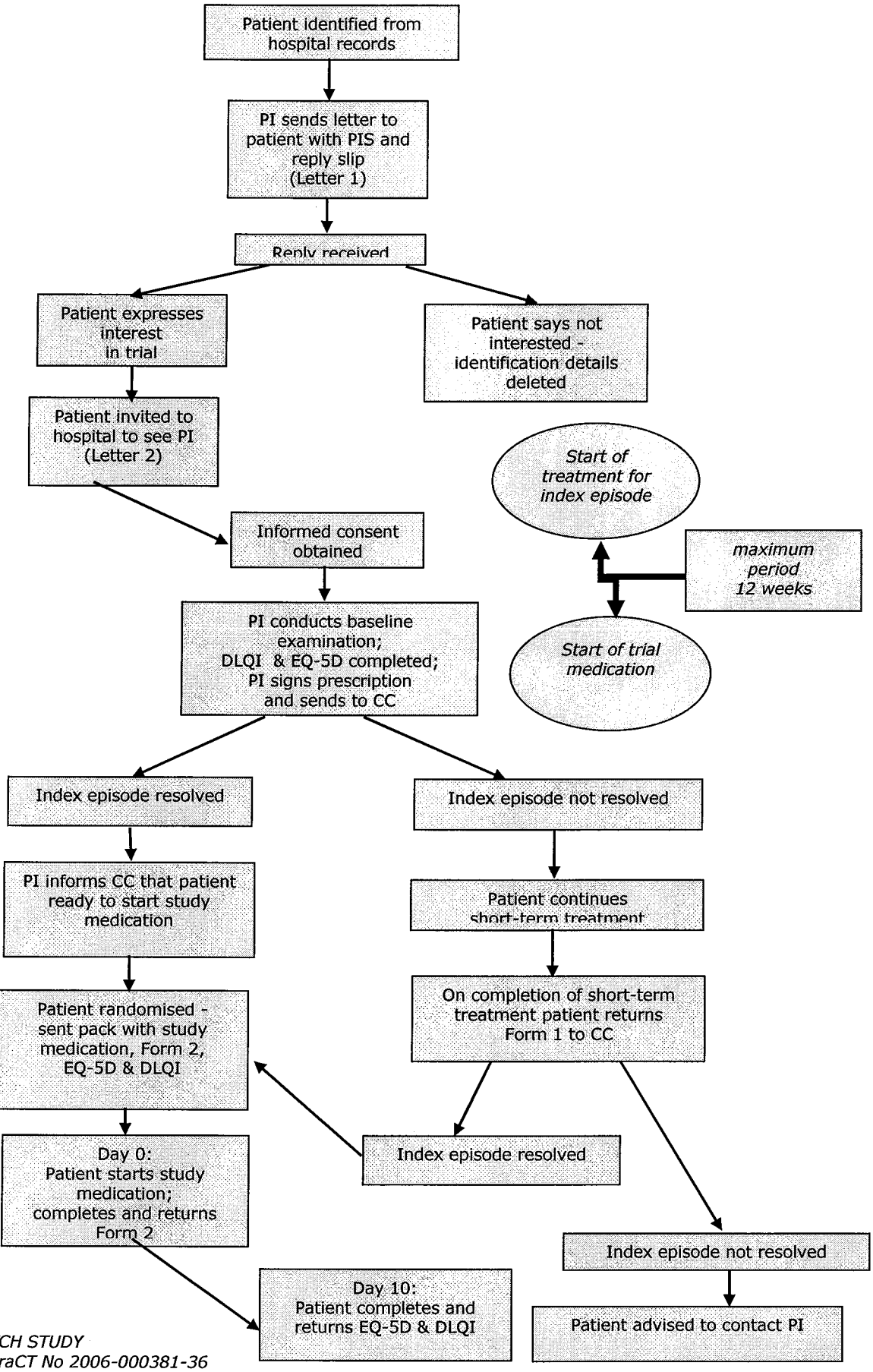
The documentation employed in the Model 3 recruitment process will be as follows:

- Advertisement/poster
- Summary participant information sheet
- Letter to patients with enclosures:
    - Summary participant information sheet with contact details
    - Reply form
    - Reply-paid addressed envelope
- Letter 2 to patient giving date and time of appointment with principal investigator
- Informed consent form
- Form 1 – (to be posted by prospective participant to the co-ordinating centre when treatment for the index episode has ended)
- Form 2 – (to be posted by participant to the co-ordinating centre to acknowledge receipt of study medication and confirm date of starting trial medication)
- DLQI and EuroQol EQ-5D
- Participant diary

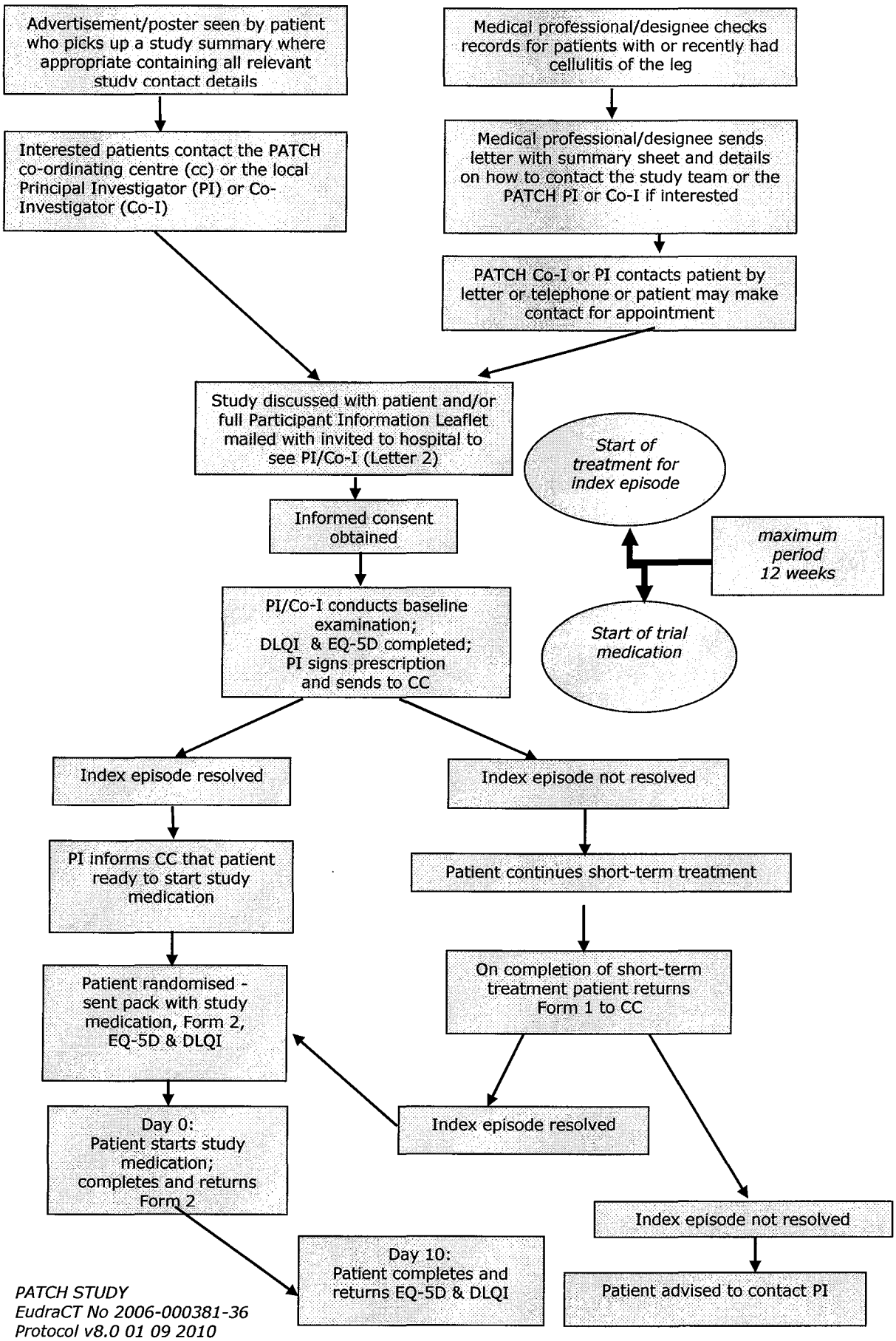
RECRUITMENT SCHEDULE FLOW CHART - MODEL 1



RECRUITMENT SCHEDULE
FLOW CHART - MODEL 2

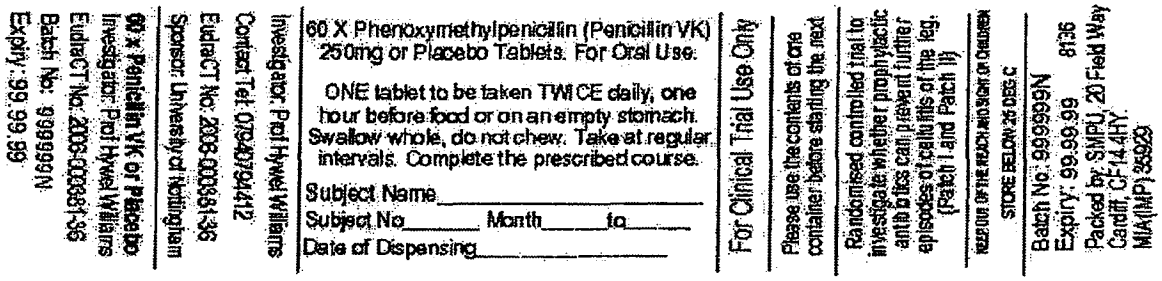


RECRUITMENT SCHEDULE FLOW CHART – MODEL 3



APPENDIX 4

TRIAL MEDICATION LABEL



ACKNOWLEDGEMENTS

Sheila Hodgson, (Clinical Trials Pharmacist at Queen's Medical Centre) has organised the supply, packaging and distribution of study medication. Dr Anne Eady (Microbiologist) and Dr Vaughan Keeley (Consultant in Palliative Medicine) have commented on the proposal. Professor James Mason (Health Economist) has offered advice on issues relating to the economic analysis of the trial. The protocol has been peer-reviewed by the Nottingham Clinical Trials Unit and by consumer advisors.

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Prophylactic Antibiotics for the Treatment of Cellulitis at Home

Prophylactic Antibiotics for the Treatment of Cellulitis at Home: PATCH

Analysis Plan for PATCH I and PATCH II

Authors:

Angela Crook, Andrew Nunn, James Mason and Kim Thomas, with contributions from the PATCH Trial Steering Committee and PATCH Data Monitoring Committee

Date approved: 13 OCTOBER 2010

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PATCH II: To determine whether 6 months of prophylaxis with penicillin VK (compared to placebo) is effective in reducing the risk of repeat episodes of cellulitis in patients who have had cellulitis of the leg **(first or recurrent episodes)**.

2.2. Secondary Objectives

(1) To determine whether protective benefits are observed only whilst treatment is maintained, or if benefits can continue in the longer term.

(2) To determine which baseline factors best predict treatment success.

(3) To assess whether prophylactic penicillin for cellulitis results in cost saving for the NHS.

(4) To evaluate whether there are any specific safety issues with regard to using Penicillin VK in this setting.

3. ENDPOINTS

3.1. Primary Endpoint

Participants will be randomised following a resolved episode of cellulitis of the leg.

The primary endpoint for both trials will be defined as the time from randomisation to next episode of clinically confirmed cellulitis as confirmed by a medically qualified person. If reviewed by more than one person, then the first medically qualified person to see the patient will take precedence as they are in a better position to document the signs of acute inflammation that could be masked by subsequent treatment.

The start date of the episode will be taken as the first date of reported symptoms by the participant.

Participants not experiencing an event will be censored at the date of their last contact in study (either end of study or when they were lost to follow-up).

3.2. Secondary Endpoints

1) Time from randomisation to next episode of cellulitis defined either as clinically confirmed or self-reported cases.

2) Number of repeat episodes of cellulitis.

3) Reduction in recurrence of cellulitis in the active treatment arm versus placebo in the treatment phase compared to the non-treatment phase.

4) Reduction in occurrences of oedema and/or ulceration in the active treatment arm versus placebo in the treatment phase compared to the non-treatment phase.

5) Predictors of response: a multiple regression model to explore the impact of known risk factors in predicting the efficacy of prophylaxis.

6) Number of serious adverse reactions considered to be related to the treatment.

7) Number of adverse events considered to be of special interest to the study: nausea, diarrhoea, thrush, rash and death.

4. SAMPLE SIZE

Previous studies have suggested a range of possible recurrence rates for patients not receiving prophylaxis of between 20 and 50%.

A 50% reduction in relapse rate in a treated group compared to no treatment was considered be the required minimum clinically relevant difference.

Therefore for PATCH I, assuming a recurrence rate of 35% in the placebo group then a total of 260 participants will be sufficient to detect a 50% reduction in recurrence rate in the penicillin VK group compared to placebo, based on a logrank test for survival analysis[2].

Similarly for PATCH II, assuming a recurrence rate of 25% in the placebo group then a total of 400 participants will be sufficient to detect a 50% reduction in recurrence rate in the penicillin VK group compared to placebo.

Both sample size calculations assume 1:1 randomisation, 5% significance (two sided), 80% power and 20% loss to follow up.

Following the decision to halt recruitment to PATCH II by the end of July 2008, the final number of participants recruited to PATCH II was 123. Under the original sample size assumptions, the power of this study was reduced to 35%.

5. ITT ANALYSIS AND MULTIPLICITY

Both PATCH trials will be analysed as intent-to-treat (ITT).

The ITT population will consist of all randomised participants with no exclusions. This will be the primary population used for the main analysis, which will use the randomised treatment allocation rather than actual treatment received.

Primary inference will be based on the primary endpoint analysis of the ITT population. Significance will be at the 5% level.

Analyses of all secondary endpoints and adjusted analyses will be considered supportive to the primary analysis so no adjustments for multiple comparisons will be made.

A secondary, modified ITT analysis of the primary endpoint will be performed excluding the following participants:

- Those who were randomised into the study, but who subsequently withdrew prior to starting treatment, (on the grounds that including these participants could dilute any observed treatment effect).
- Those who reported a relapse within 4 weeks of randomisation, (on the grounds that it is likely that such “relapses” reflect incomplete treatment of the index episode rather than a true recurrence).

6. STRATA AND COVARIATES

6.1. Stratification variables

For both studies, randomisation will be stratified by the following:

- Presence of pre-existing oedema;

- Presence of ulcer subsequent to the cellulitis;
- Presence of pre-existing oedema and presence of ulcer subsequent to the cellulitis
- No pre-existing oedema or ulcer subsequent to the cellulitis

In addition, for PATCH II, an initial stratification of the following will take place:

- First episode of cellulitis;
- More than one previous episode of cellulitis.

For the primary endpoint an adjusted analysis including these stratification variables will be performed and the results reported alongside the main unadjusted findings.

6.2. Other covariates

The following baseline covariates will be used to investigate the predictors of response model.

- Age
- Sex
- Body Mass Index (BMI)
- History of cellulitis
- Asymmetrical chronic oedema / lymphoedema
- Symmetrical chronic oedema / lymphoedema
- Venous insufficiency
- Leg ulcer subsequent to cellulitis
- Tinea pedis/Toeweb maceration
- Preceding surgery to the leg
- Blunt injury
- IV drug abuse
- Diabetes
- Onychomycosis

- Ethnicity (for PATCH I only)

7. ADDITIONAL ANALYSES

Subgroup analysis

There had been one planned subgroup analyses for the PATCH II study of patients with recurrent cellulitis. Assuming the same relapse rate as for PATCH I, there would have been sufficient power to perform this planned subgroup analysis had the study reached the recruitment target of 400 patients. However following the decision to halt recruitment to PATCH II by end of July 2008, with n=123 participants, there will not be sufficient power to perform this subgroup analysis.

No additional subgroup analyses were planned for this study.

Sensitivity Analysis

A sensitivity analysis of the treatment effect will be performed for the primary endpoint restricted to patients who started treatment more than 12 weeks prior to randomisation.

A further sensitivity analysis of the treatment effect will be performed for the primary endpoint restricted to those patients identified from primary care/advertising and compared to those identified within secondary care.

8. DATA HANDLING

Partial dates: For partial dates, missing months will be taken as June and missing days will be taken as the 15th day of the month.

Missing data: As a a time-to-event analysis an outcome for each patient will be determined as either having a recurrence of cellulitis at or before their last date of contact or not. The adjusted analysis will use the stratification variables which will be 100% complete by definition.

Loss to follow-up will be summarised graphically by treatment group.

Covariates

Age (in years) for both studies will be calculated at randomisation.

Body mass index (BMI) will be calculated as:

$$\text{Body Mass Index } (\text{kg/m}^2) = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$$

The EQ-5D patient questionnaire scores will be converted to health preference scores using the social tariff algorithm provided by the Euroqol group.

Data quality

Data queries will be resolved at data entry using a query form. To minimise errors, 100% of stratification variables and recurrence data will be verified by a data entry clerk who did not originally enter the data. A 10 % sample of all other data will be checked for accuracy.

9. BASELINE CHARACTERISTICS

Demographic, clinical history and other baseline characteristics (listed in Section 6) will be cross-tabulated against randomised treatment allocation to check for appropriate balance. No formal statistical tests will be performed.

10. TREATMENT COMPLIANCE AND WITHDRAWALS

Compliance to treatment will be measured from patient diaries and follow up telephone calls. Treatment compliance will be defined as those participants who report taking treatment *as intended* to the end of the treatment phase or to recurrence of cellulitis (if this occurs before the end of the treatment phase). This will include times when a patient interrupts study drug for medicinal purposes.

Compliance will be categorised as follows:

4 = All taken (75 - 100 %)
3 = Most taken (50 – 74 %)
2 = Some taken (25 – 49 %)
1 = Hardly any taken (1 – 24 %)
0 = None taken

This will be summarised (n, %) by randomised treatment allocation. Reasons for non-compliance will also be summarised by randomised treatment allocation. Compliance will also be summarised at different time points to investigate whether there is any drop in compliance over time.

Duration of treatment will be measured from date of randomisation to date treatment stopped and will be summarised (mean, SD and range) by randomised treatment allocation.

The number of participants withdrawing from the study including reasons for withdrawal will be summarised (n, %) by randomised treatment allocation.

11. STATISTICAL ANALYSES

11.1. Primary endpoint analyses

For both studies, survival analysis will be used for the time-to-event endpoints.

A Cox proportional hazards model will be used to analyse the primary endpoint, time to first recurrence of confirmed episode of cellulitis.

Treatment effects from the model will be summarised by hazard ratios (HR) with reference to the placebo group.

i.e. HR <1 will indicate a protective effect of the VK penicillin compared to placebo.

Unadjusted and adjusted HRs with 95% confidence intervals and p-values will be presented.

Inference will be made from the unadjusted analysis. The unadjusted analysis will only include treatment group in the model. The adjusted analyses will include treatment group and the relevant stratification variables.

For each study, a Kaplan Meier curve will be constructed indicating separate curves for the different treatment groups.

These analyses assume the prophylactic effect is constant over time. This proportional hazards assumption will be assessed. If the model appears to be inadequate an alternative survival model will be considered.

11.2. Secondary endpoint analyses

1. The secondary (time-to-event) endpoint, including the unconfirmed cellulitis episodes, will be analysed in a similar way to the primary endpoint.

2. The number of repeat episodes (0,1,2,3…) will be summarised (n,%) by randomised treatment allocation and overall.

The proportion of participants reporting multiple episodes (0,1,2 etc) will be compared across treatment groups by use of the Chi-Square test for trend.

3. The number and percentage of participants with repeat of episodes of cellulitis on active treatment versus placebo will be summarised by treatment phase and overall.

A piece-wise Cox model analysis will also be performed to estimate the effect of treatment during the treatment phase and post treatment phase. The results will be displayed graphically as a Forrest plot.

4. The number and percentage of participants with oedema and/or ulceration on active treatment group versus placebo will be summarised by treatment phase and overall. This will also be displayed graphically.

5. Responders to treatment will be defined as those participants not experiencing a recurrence of cellulitis during the trial. The predictors of response model will be analysed as a binary response, where an event is *no* recurrence, in order to simplify the interpretation of parameter estimates. Therefore multiple logistic regression models will be used to determine specific patient groups most likely to benefit from treatment.

Risk factors listed in Section 6 will be included in the models to determine their effect on response. If appropriate, separate models will be considered for ipsilateral and contra-lateral episodes.

Note that this analysis will not be performed if no treatment effect is observed in the primary analysis – that is if neither the unadjusted nor the adjusted analysis shows a significant effect of penicillin over placebo.

6. Serious adverse reactions will be summarised (n,%) and listed by treatment allocation. Severity of event and event duration will be included in the line listing.

7. Other adverse events considered to be of special interest to this study will be summarised (n,%) and listed by treatment allocation. Relationship to treatment, severity or event and event duration will be included in the line listing.

PATCH I and PATCH II data will be considered for use in future meta-analyses.

12. COST EFFECTIVENESS

All analyses will be at the patient level and by intention to treat. Economic analyses will take a NHS perspective. Sensitivity analysis will explore findings from an NHS perspective.

Health service resource measures. Numbers of: days spent in hospital (sub-divided by level of care: intensive, high dependency, general); outpatient visits; GP consultations; courses of antibiotics prescribed for the treatment of cellulitis; and related investigations will be reported and analysed. Resource measures often present skewed distributions. Where parametric test assumptions are not validated, Mann-Whitney U tests will be used to test differences.

Indirect costs of care. Following each occurrence of cellulitis, patients will be surveyed for time off work or away from routine activities, where the patient attributes these to the episode of cellulitis.

Average cost of care. If differences in resource measures are demonstrated between groups, differences in cost will be analysed.

Healthcare resource measures will be costed using published national reference costs [3-5]. Differences in average costs between groups will be compared and confidence intervals estimated using bootstrap methods [6].

Cost-effectiveness. If differences in cellulitis episodes are demonstrated between groups, then the primary cost-effectiveness analysis will be cost per episode of cellulitis prevented. Additionally the impact upon quality of life will be analysed. Patient-level cost-effectiveness estimates will be used to generate cost-effectiveness planes and acceptability curves for antibiotic prophylaxis PATCH-I and PATCH-II populations using standard stochastic methods [7].

Economic analysis will be performed in Excel.

13. IMPACT OF CELLULITIS ON HEALTH RELATED QUALITY OF LIFE

Data from both trials (on completion of PATCH I) will be combined for analysis to assess the impact of cellulitis on Health Related Quality of Life (HRQoL).

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14. SIGNATURES

Professor H. Williams	
Professor A. J. Nunn	
Dr A. Crook	
Dr K. S. Thomas	
Professor J. Mason	

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7) Number of adverse events considered to be of special interest to the study: nausea, diarrhoea, thrush, rash and death.

4. SAMPLE SIZE

Previous studies have suggested a range of possible recurrence rates for patients not receiving prophylaxis of between 20 and 50%.

A 50% reduction in relapse rate in a treated group compared to no treatment was considered be the required minimum clinically relevant difference.

Therefore for PATCH I, assuming a recurrence rate of 35% in the placebo group then a total of 260 participants will be sufficient to detect a 50% reduction in recurrence rate in the penicillin VK group compared to placebo, based on a logrank test for survival analysis[2].

Similarly for PATCH II, assuming a recurrence rate of 25% in the placebo group then a total of 400 participants will be sufficient to detect a 50% reduction in recurrence rate in the penicillin VK group compared to placebo.

Both sample size calculations assume 1:1 randomisation, 5% significance (two sided), 80% power and 20% loss to follow up.

Following the decision to halt recruitment to PATCH II by the end of July 2008, the final number of participants recruited to PATCH II was 123. Under the original sample size assumptions, the power of this study was reduced to 35%.

5. ITT ANALYSIS AND MULTIPLICITY

Both PATCH trials will be analysed as intent-to-treat (ITT).

The ITT population will consist of all randomised participants with no exclusions. This will be the primary population used for the main analysis, which will use the randomised treatment allocation rather than actual treatment received.

Primary inference will be based on the primary endpoint analysis of the ITT population. Significance will be at the 5% level.

Analyses of all secondary endpoints and adjusted analyses will be considered supportive to the primary analysis so no adjustments for multiple comparisons will be made.

A secondary, modified ITT analysis of the primary endpoint will be performed excluding the following participants:

- Those who were randomised into the study, but who subsequently withdrew prior to starting treatment, (on the grounds that including these participants could dilute any observed treatment effect).
- Those who reported a relapse within 4 weeks of randomisation, (on the grounds that it is likely that such “relapses” reflect incomplete treatment of the index episode rather than a true recurrence).

6. STRATA AND COVARIATES

6.1. Stratification variables

For both studies, randomisation will be stratified by the following:

- Presence of pre-existing oedema;

- Presence of ulcer subsequent to the cellulitis;
- Presence of pre-existing oedema and presence of ulcer subsequent to the cellulitis
- No pre-existing oedema or ulcer subsequent to the cellulitis

In addition, for PATCH II, an initial stratification of the following will take place:

- First episode of cellulitis;
- More than one previous episode of cellulitis.

For the primary endpoint an adjusted analysis including these stratification variables will be performed and the results reported alongside the main unadjusted findings.

6.2. Other covariates

The following baseline covariates will be used to investigate the predictors of response model.

- Age
- Sex
- Body Mass Index (BMI)
- History of cellulitis
- Asymmetrical chronic oedema / lymphoedema
- Symmetrical chronic oedema / lymphoedema
- Venous insufficiency
- Leg ulcer subsequent to cellulitis
- Tinea pedis/Toeweb maceration
- Preceding surgery to the leg
- Blunt injury
- IV drug abuse
- Diabetes
- Onychomycosis

- Ethnicity (for PATCH I only)

7. ADDITIONAL ANALYSES

Subgroup analysis

There had been one planned subgroup analyses for the PATCH II study of patients with recurrent cellulitis. Assuming the same relapse rate as for PATCH I, there would have been sufficient power to perform this planned subgroup analysis had the study reached the recruitment target of 400 patients. However following the decision to halt recruitment to PATCH II by end of July 2008, with n=123 participants, there will not be sufficient power to perform this subgroup analysis.

No additional subgroup analyses were planned for this study.

Sensitivity Analysis

A sensitivity analysis of the treatment effect will be performed for the primary endpoint restricted to patients who started treatment more than 12 weeks prior to randomisation.

A further sensitivity analysis of the treatment effect will be performed for the primary endpoint restricted to those patients identified from primary care/advertising and compared to those identified within secondary care.

8. DATA HANDLING

Partial dates: For partial dates, missing months will be taken as June and missing days will be taken as the 15th day of the month.

Missing data: As a a time-to-event analysis an outcome for each patient will be determined as either having a recurrence of cellulitis at or before their last date of contact or not. The adjusted analysis will use the stratification variables which will be 100% complete by definition.

Loss to follow-up will be summarised graphically by treatment group.

Covariates

Age (in years) for both studies will be calculated at randomisation.

Body mass index (BMI) will be calculated as:

$$\text{Body Mass Index } (\text{kg/m}^2) = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$$

The EQ-5D patient questionnaire scores will be converted to health preference scores using the social tariff algorithm provided by the Euroqol group.

Data quality

Data queries will be resolved at data entry using a query form. To minimise errors, 100% of stratification variables and recurrence data will be verified by a data entry clerk who did not originally enter the data. A 10 % sample of all other data will be checked for accuracy.

9. BASELINE CHARACTERISTICS

Demographic, clinical history and other baseline characteristics (listed in Section 6) will be cross-tabulated against randomised treatment allocation to check for appropriate balance. No formal statistical tests will be performed.

10. TREATMENT COMPLIANCE AND WITHDRAWALS

Compliance to treatment will be measured from patient diaries and follow up telephone calls. Treatment compliance will be defined as those participants who report taking treatment *as intended* to the end of the treatment phase or to recurrence of cellulitis (if this occurs before the end of the treatment phase). This will include times when a patient interrupts study drug for medicinal purposes.

Compliance will be categorised as follows:

4 = All taken (75 - 100 %)
3 = Most taken (50 – 74 %)
2 = Some taken (25 – 49 %)
1 = Hardly any taken (1 – 24 %)
0 = None taken

This will be summarised (n, %) by randomised treatment allocation. Reasons for non-compliance will also be summarised by randomised treatment allocation. Compliance will also be summarised at different time points to investigate whether there is any drop in compliance over time.

Duration of treatment will be measured from date of randomisation to date treatment stopped and will be summarised (mean, SD and range) by randomised treatment allocation.

The number of participants withdrawing from the study including reasons for withdrawal will be summarised (n, %) by randomised treatment allocation.

11. STATISTICAL ANALYSES

11.1. Primary endpoint analyses

For both studies, survival analysis will be used for the time-to-event endpoints.

A Cox proportional hazards model will be used to analyse the primary endpoint, time to first recurrence of confirmed episode of cellulitis.

Treatment effects from the model will be summarised by hazard ratios (HR) with reference to the placebo group.

i.e. HR <1 will indicate a protective effect of the VK penicillin compared to placebo.

Unadjusted and adjusted HRs with 95% confidence intervals and p-values will be presented.

Inference will be made from the unadjusted analysis. The unadjusted analysis will only include treatment group in the model. The adjusted analyses will include treatment group and the relevant stratification variables.

For each study, a Kaplan Meier curve will be constructed indicating separate curves for the different treatment groups.

These analyses assume the prophylactic effect is constant over time. This proportional hazards assumption will be assessed. If the model appears to be inadequate an alternative survival model will be considered.

11.2. Secondary endpoint analyses

1. The secondary (time-to-event) endpoint, including the unconfirmed cellulitis episodes, will be analysed in a similar way to the primary endpoint.

2. The number of repeat episodes (0,1,2,3…) will be summarised (n,%) by randomised treatment allocation and overall.

The proportion of participants reporting multiple episodes (0,1,2 etc) will be compared across treatment groups by use of the Chi-Square test for trend.

3. The number and percentage of participants with repeat of episodes of cellulitis on active treatment versus placebo will be summarised by treatment phase and overall.

A piece-wise Cox model analysis will also be performed to estimate the effect of treatment during the treatment phase and post treatment phase. The results will be displayed graphically as a Forrest plot.

4. The number and percentage of participants with oedema and/or ulceration on active treatment group versus placebo will be summarised by treatment phase and overall. This will also be displayed graphically.

5. Responders to treatment will be defined as those participants not experiencing a recurrence of cellulitis during the trial. The predictors of response model will be analysed as a binary response, where an event is *no* recurrence, in order to simplify the interpretation of parameter estimates. Therefore multiple logistic regression models will be used to determine specific patient groups most likely to benefit from treatment.

Risk factors listed in Section 6 will be included in the models to determine their effect on response. If appropriate, separate models will be considered for ipsilateral and contra-lateral episodes.

Note that this analysis will not be performed if no treatment effect is observed in the primary analysis – that is if neither the unadjusted nor the adjusted analysis shows a significant effect of penicillin over placebo.

6. Serious adverse reactions will be summarised (n,%) and listed by treatment allocation. Severity of event and event duration will be included in the line listing.

7. Other adverse events considered to be of special interest to this study will be summarised (n,%) and listed by treatment allocation. Relationship to treatment, severity or event and event duration will be included in the line listing.

PATCH I and PATCH II data will be considered for use in future meta-analyses.

12. COST EFFECTIVENESS

All analyses will be at the patient level and by intention to treat. Economic analyses will take a NHS perspective. Sensitivity analysis will explore findings from an NHS perspective.

Health service resource measures. Numbers of: days spent in hospital (sub-divided by level of care: intensive, high dependency, general); outpatient visits; GP consultations; courses of antibiotics prescribed for the treatment of cellulitis; and related investigations will be reported and analysed. Resource measures often present skewed distributions. Where parametric test assumptions are not validated, Mann-Whitney U tests will be used to test differences.

Indirect costs of care. Following each occurrence of cellulitis, patients will be surveyed for time off work or away from routine activities, where the patient attributes these to the episode of cellulitis.

Average cost of care. If differences in resource measures are demonstrated between groups, differences in cost will be analysed.

Healthcare resource measures will be costed using published national reference costs [3-5]. Differences in average costs between groups will be compared and confidence intervals estimated using bootstrap methods [6].

Cost-effectiveness. If differences in cellulitis episodes are demonstrated between groups, then the primary cost-effectiveness analysis will be cost per episode of cellulitis prevented. Additionally the impact upon quality of life will be analysed. Patient-level cost-effectiveness estimates will be used to generate cost-effectiveness planes and acceptability curves for antibiotic prophylaxis PATCH-I and PATCH-II populations using standard stochastic methods [7].

Economic analysis will be performed in Excel.

13. IMPACT OF CELLULITIS ON HEALTH RELATED QUALITY OF LIFE

Data from both trials (on completion of PATCH I) will be combined for analysis to assess the impact of cellulitis on Health Related Quality of Life (HRQoL).

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[7] Briggs A, Fenn P. Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. Health Econ. 1998 Dec;7(8):723-40.

14. SIGNATURES

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7. ADDITIONAL ANALYSES

This incorrectly states:

A sensitivity analysis of the treatment effect will be performed for the primary endpoint restricted to patients who started treatment more than 12 weeks prior to **randomisation**.

In line with the study protocol the correct version should state:

A sensitivity analysis of the treatment effect will be performed for the primary endpoint restricted to patients who started treatment more than 12 weeks prior to the **baseline visit.**

This point was discussed at a teleconference between, Angela Crook (trial statistician), Kim Thomas (lead investigator) and Kath Foster (trial manager) on the 18th November 2010 and agreed that an addendum would be sufficient.