Study of Treatments for Pyoderma Gangrenosum Patients (STOP GAP) – an RCT of oral prednisolone versus ciclosporin

Final Version 4.0

30 August 2011

Short title:	RCT of treatments for pyoderma gangrenosum
Acronym:	STOP GAP
EudraCT number:	2008-008291-14
ISRCTN:	ISRCTN35898459
CTA reference:	19162/0213/001
MREC reference:	09/H0903/5
UK CRN reference:	5692
Trial Sponsor:	Nottingham University Hospitals NHS Trust
Funding Source:	National Institute for Health Research (NIHR)

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1. TRIAL PERSONNEL AND CONTACT DETAILS

Sponsor:	**Nottingham University Hospitals NHS Trust** Contact name: Dr Maria Koufali Deputy Director Research & Innovation Nottingham Health Science Partners C Floor, South Block Queens Medical Centre Nottingham NG7 2UH **Phone:** 0115 601159249924 ext 70676 **Fax:** 0115 8493295 **Email:** maria.koufali@nuh.nhs.uk
Chief investigator:	**Professor Hywel Williams** Professor of Dermato-epidemiology Dermatology Department South Block Queen's Medical Centre Nottingham NG7 2UH **Phone:** 0115 823 1048 **Fax:** 0115 823 1046 **Email:** hywel.williams@nottingham.ac.uk
Lead Clinician	**Dr Anthony Ormerod** Consultant Dermatologist Department of Medicine and Therapeutics Polwarth Building Aberdeen Royal Infirmary Foresterhill Aberdeen, AB24 2ZD **Phone:** 01224 553955 **Fax:** 01224 550555 **Email:** A.D.Ormerod@arh.grampian.scot.nhs.uk
Trial Manager	**Eleanor Mitchell** Nottingham Clinical Trials Unit Nottingham Health Science Partners C Floor, South Block Queens Medical Centre Nottingham NG7 2UH **Phone: 0115 8844926** **Fax: 0115 9194430** **Email:** eleanor.mitchell@nottingham.ac.uk
Trial Administrator	**Julie Barnes** Nottingham Clinical Trials Unit Nottingham Health Science Partners C Floor, South Block Queens Medical Centre Nottingham NG7 2UH **Phone: 0115 8844941** **Fax: 0115 9194430** **Email:** j.barnes@nottingham.ac.uk
Trial Statistician	**Professor John Norrie** Chair in Clinical Trials and Biostatistics Robertson Centre for Biostatistics University of Glasgow Boyd Orr Building University Avenue Glasgow G12 8QQ **Phone:** 0141 330 4744 **Fax:** 0141 330 5094 **Email:** johnn@stats.gla.ac.uk
Data Management	**Daniel Simpkins and Keith Whittaker** Nottingham Clinical Trials Unit Nottingham Health Science Partners

	C Floor, South Block Queens Medical Centre Nottingham NG7 2UH **Phone:** 0115 8844935 **Email:** daniel.simpkins@nottingham.ac.uk
Trial Health Economist	**Professor James Mason & junior health economist (to be appointed)** Professor of Health Economics Wolfson Research Institute University of Durham, Queen's Campus University Boulevard Stockton-on-Tees TS17 6BH Phone: 0191 334 0324 Fax: 0191 334 0324 Email: j.m.mason@durham.ac.uk
Trial Pharmacist	**Sheila Hodgson** Clinical Trials Pharmacist Nottingham University Hospitals NHS Trust QMC campus Derby Road Nottingham NG7 2UH Phone: 0115 9194450 Email: Sheila.Hodgson@nuh.nhs.uk
Trial Coordinating Centre:	**UK Dermatology Clinical Trials Network** Centre of Evidence based Dermatology University of Nottingham King's Meadow Campus Lenton Lane Nottingham NG7 2NR and Nottingham Clinical Trials Unit Nottingham Health Science Partners C Floor, South Block Queens Medical Centre Nottingham NG7 2UH
Programme Manager:	**Dr Kim Thomas** UK Dermatology Clinical Trials Network Centre of Evidence based Dermatology University of Nottingham King's Meadow Campus Lenton Lane Nottingham NG7 2NR Phone: 0115 8468632 Fax: 0115 8468618 Email: kim.thomas@nottingham.ac.uk
Digital Image Analysis:	Nottingham Clinical Trials Unit Nottingham Health Science Partners C Floor, South Block Queens Medical Centre Nottingham NG7 2UH

2. SYNOPSIS

Title	Study of Treatments for Pyoderma GAngrenosum Patients – an RCT of oral prednisolone versus ciclosporin
Acronym	STOP GAP
Short title	RCT of treatments for pyoderma gangrenosum
Chief Investigator	Professor Hywel Williams
Objectives	To assess whether systemic ciclosporin 4 mg/kg/day is more effective than systemic prednisolone 0.75 mg/kg/day for oral therapy of PG.
Trial Configuration	Prospective, 2-arm, single-blind, parallel group RCT - with parallel observational study of topical therapy for patients who are not yet suitable for systemic therapy.
Setting	Secondary care – UK and Ireland (additional European countries may be added depending on recruitment success)
Sample size estimate	One hundred and forty patients in total (randomised 1:1 to systemic prednisolone or systemic ciclosporin) will give the study at least 80% power at a 5% level of significance using a two sided two sample t-test to detect a difference in means of 0.5 standard deviations of the primary outcome of velocity of healing at 6 weeks. The velocity of healing at week 6 is defined as the percentage change in surface area (measured by planimetry using digital photographs) over baseline of the target lesion. This sample size allows for an approximate 10% loss to follow up at 6 weeks.
Number of participants	140
Eligibility criteria	Patients with a presumed diagnosis of PG will be contacted about the study. The following inclusion criteria will apply. • PG as diagnosed by the recruiting dermatologist. [An ulcerative lesion may have mixed aetiology, but provided the investigator has confidence that a clinical diagnosis of PG is appropriate then they are eligible. Other contributing factors and atypical features will be captured in the case report form]. • Age over 18 years. • Able to provide written, informed consent.
Description of interventions	Oral ciclosporin 4 mg/kg/day is compared with oral prednisolone 0.75 mg/kg/day (up to a ceiling dose of 75 mg/day prednisolone and 400 mg/day ciclosporin).
Duration of study	Participants are enrolled until the ulcer has healed, or for a period of 6 months, which ever is sooner. Recruitment is planned to start April 2009 (depending on approvals).
Randomisation and blinding	Participants will be randomised to treatment allocation using a computer-generated pseudo-random list using permuted blocks of randomly varying size between 2 & 6, created using the ralloc Stata add-on. Randomisation will be stratified by lesion size (lesions ≥ $20cm^2$ versus lesions $<20cm^2$) and presence or absence of underlying systemic disease (e.g. inflammatory bowel disease). The randomisation sequence will be concealed until interventions are all assigned and recruitment, data collection, and data cleaning are complete. Accessing the randomisation code will be flexible according to local needs. This may include:

	• Clinical trials pharmacist (using a pre-prepared randomisation schedule or web-based randomisation) • Recruiting physician / designee (using telephone, text or web-based randomisation)
Outcome measures	Primary outcome measure: • velocity of healing Secondary outcome measures: • Time to healing • Global assessment of improvement (PG specific) • Inflammation assessment scale • Self-reported pain • Impact on health related quality of life • Time to recurrence • Number of treatment failures • Adverse reactions to study medications • Cost-effectiveness
Statistical methods	The primary analysis will be according to the intention to treat principle, and will adjust for known prognostic baseline co-variates. All analyses will be fully specified in a Statistical Analysis Plan, to be agreed before unblinding the data by the Trial Steering Committee. The influence of missing data will be examined using multiple imputation techniques. There are no formal planned interim analyses, but progress reports on all data issues will be presented to a Data Monitoring Committee, who will agree their charter at their first meeting.

3. ABBREVIATIONS

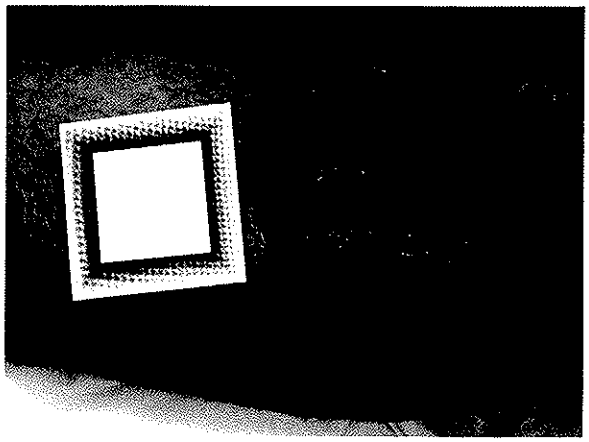
ADR	Adverse Drug Reaction
AE	Adverse Event
CI	Chief Investigator overall
CRF	Case Report Form
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
IMB	Irish Medicines Board
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
PG	Pyoderma gangrenosum
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

4. TRIAL BACKGROUND INFORMATION AND RATIONALE

4.1 Background to the condition

Pyoderma gangrenosum (PG) is a mutilating, very painful skin disease that often affects people with an underlying internal disease (such as inflammatory bowel disease, monoclonal gammopathy and rheumatoid arthritis). It starts as a reddish purple bump in the skin that develops into a large, deep, spreading ulcer in a matter of days. People with PG are often misdiagnosed, and spend a long time in hospital waiting for the affected areas to heal (ulcers can last for a variable time on average healing after 3-4 months). Patients are not able to work, require daily dressings, have a high need for health care resources, and have very poor quality of life. Patients often have repeat episodes of PG and may have multiple lesions.

Figure 1 Pyoderma gangrenosum



Treatment of PG usually involves immunosuppression or immunomodulation. A recent systematic review(1) recommended the use of prednisolone, ciclosporin or high dose intravenous steroids for large lesions; or potent topical steroids, tacrolimus or intralesional steroid injection for small lesions. However, these recommendations were based on case series alone as no RCTs of these most commonly used treatments were identified. Many of these treatments are associated with unpleasant and damaging side-effects, making their formal evaluation a matter of urgency. These treatments are currently being used for patients with PG without rigorous testing or understanding of their relative efficacy, cost and side-effect profile.

An audit was recently conducted by the UK Dermatology Clinical Trials Network of all cases of PG occurring in 11 centres over 3 years. This has shown 188 episodes of PG occurring in 155 patients. Patients required an average of 2 treatments per episode. 22% of episodes were treated solely with topical treatment; the remaining 78% required systemic treatments, either alone or in combination with topical treatment. The most commonly used systemic treatments were prednisolone (in 56%), ciclosporin

(29%), tetracyclines (20%), biologics (9%) and azathioprine (8%). 56% of episodes were documented as having healed, in a median time of 5 months.

The unique opportunity to investigate this condition by recruiting through the UK Dermatology Clinical Trials Network means that formal evaluation of systemic treatments within a randomised controlled trial is now possible for the first time. The Network will also be instrumental in ensuring that the results of this trial translate to changes in clinical practice.

4.2 What is the question to be addressed?

This study seeks to address the lack of evidence for the treatment of patients with PG. It will compare head-to-head the two most commonly used systemic treatments – see Figure 1. Oral prednisolone (gold standard for patients requiring systemic therapy), will be compared with ciclosporin. As this is a relatively rare condition, patients who initially require topical therapy will be asked to enter a parallel observational study and outcome data will be collected over the study period. Should the ulcer(s) fail to respond to topical therapy, then participants will be asked to take part in the randomised trial of systemic treatments.

5. DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

5.1 Description

This study will compare two active medications that are both used in everyday practice for the treatment of PG:

- Prednisolone available in either tablets or dispersible tablets.
- Ciclosporin (Neoral®) available in either capsules or oral solution.

Participants will be prescribed study medication from the standard pharmacy supplies, so any brand of prednisolone may be prescribed. However, the bioavailability of ciclosporin varies depending on the brand used. For the purposes of this trial, Neoral® (Novartis) will be used.

More details regarding the chemical and pharmacological properties of the study drugs can be found in the Summary of Product Characteristics.

5.2 Known Side Effects

Prednisolone

Gastro-Intestinal Dyspepsia, peptic ulceration with perforation and haemorrhage, abdominal distension, oesophageal ulceration, oesophageal candidiasis, acute pancreatitis, perforation of bowel, gastric haemorrhage.

Increases in alanine transaminase (ALT, SGPT) aspartate transaminase (AST, SGOT) and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.

Anti-Inflammatory And Immunosuppressive Effects Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, may suppress reactions to skin tests, recurrence of dormant tuberculosis (see Special warnings and special precautions for use).

Musculoskeletal Proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture, muscle weakness.

Fluid And Electrolyte Disturbance Sodium and water retention, hypertension, hypokalaemic alkalosis, potassium loss, congestive heart failure in susceptible patients.

Dermatological Impaired healing, skin atrophy, bruising, striae, telangiectasia, acne, petechiae and ecchymosis. Kaposi's sarcoma has been reported.

Endocrine/Metabolic Suppression of the hypothalamo - pituitary-adrenal axis, growth suppression in infancy, childhood and adolescence; menstrual irregularity and amenorrhoea. Cushingoid facies, hirsutism, weight gain, impaired carbohydrate tolerance with increased requirement for antidiabetic therapy, negative nitrogen and calcium balance. Increased appetite.

Neuropsychiatric A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood psychological dependence and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, seizures and cognitive dysfunction including confusion and amnesia have been reported for all corticosteroids. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions was estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown. Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri) has been reported, usually after treatment withdrawal of methylprednisolone.

Ophthalmic Increased intra - ocular pressure, glaucoma, papilloedema with possible damage to the optic nerve, cataracts, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal disease, exophthalmos.

Cardiovascular Myocardial rupture following myocardial infarction.

General Leucocytosis, hypersensitivity reactions including anaphylaxis, thrombo-embolism, nausea, malaise, persistent hiccups with high doses of corticosteroids.

Withdrawal Symptoms Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (see Special warnings and special precautions for use). A 'withdrawal syndrome' may also occur including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

Ciclosporin

Many side effects associated with ciclosporin therapy are dose-dependent and responsive to dose reduction. In the various indications the overall spectrum of side-effects is essentially the same; there are, however, differences in incidence and severity. The details below ranks adverse reactions to ciclosporin under frequency, the most frequent first, using the following convention: very common (≥ 1/10) ; common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, <1/100); rare (≥ 1/10,000 <1/1000); very rare (< 1/10,000), including isolated reports.

Infections and infestations: patients receiving ciclosporin and ciclosporin-containing regimens as well as other immunosuppressive regimens are at increased risk of infections (viral, bacterial, fungal, parasitic). Both generalised and localised infections can occur. Pre-existing infections may also be aggravated. Fatal outcomes have been reported. The most important infections observed during long-term post-marketing surveillance of solid-orgal transplants were;
Very common: lower respiratory tract infection including cases of bronchiolitis, urinary tract infection, cytomegalovirus infection, upper respiratory tract infection.
Common: sepsis, herpes infections, candidal infection.

Neoplasms benign, malignant and unspecified (including cysts and polyps): the increased risk of developing malignancies and lymphoproliferative disorders (including lymphomas), some with reported fatalities, appears to be related to the degree and duration of immunosuppression rather than to the use of specific agents. The most frequently observed neoplasms during long-term post-marketing surveillance were:
Common: skin papillomas, basal cell carcinoma, squamous cell carcinoma of skin, Bowen's disease, lymphoproliferative disorders.
Uncommon: seborrhoeic keratosis, melanoma, squamous cell carcinoma.

Blood and lymphatic system disorders: *uncommon:* anaemia, thrombocytopenia, *rare:* microangiopathic haemolytic anaemia, haemolytic uraemic syndrome.

Metabolism and nutrition disorders: *very common:* hyperlipidaemia, hypercholesterolaemia. *Common:* anorexia, hyperuricaemia, hyperkalaemia, hypomagnesaemia, *Rare:* hyperglycaemia.

Nervous system disorders: *Very common:* tremor, headache. *Common:* paraesthesia. *Uncommon:* signs of encephalopathy such as; convulsions, confusion, disorientation, decreased responsiveness, agitation, insomnia, visual disturbances, cortical blindness, coma, paresis, cerebellar ataxia. *Rare:* Motor polyneuropathy. *Very rare:* optic disc oedema including papilloedema with possible visual impairment secondary to benign intracranial hypertension.

Vascular disorders: *very common:* hypertension

Gastrointestinal disorders: *Common:* nausea, vomiting, abdominal pain, diarrhoea, gingival hyperplasia, *Rare:* pancreatitis.

Hepatobiliary disorders: *Common:* hepatic dysfunction

Skin and subcutaneous tissue disorders: *Common:* hypertrichosis. *Uncommon:* allergic rashes

Musculoskeletal and connective tissue disorders: *Common:* muscle cramps, myalgia, *Rare:* muscle weakness, myopathy.

Renal and urinary disorders: *Very common:* renal dysfunction

Reproductive system and breast disorders: *Rare:* menstrual disturbances, gynecomastia.

General disorders: *Common:* fatigue. *Uncommon:* oedema, weight increase.

6. TRIAL / STUDY OBJECTIVES AND PURPOSE

6.1 Purpose

To evaluate the efficacy and safety of the two most commonly used systemic treatments for PG. The study aims to test the hypothesis that systemic ciclosporin (4 mg/kg/day) is more effective than systemic prednisolone (0.75 mg/kg/day) for oral therapy of PG. A ceiling daily dose of prednisolone (75 mg) and ciclosporin (400 mg) will be imposed.

6.2 Hypothesis

The hypothesis for this study is that:

- Ciclosporin gains control of the disease more rapidly, and reduces the time to healing for patients with PG compared to treatment with oral prednisolone.

6.3 Primary Objective

- To assess the speed of response to treatment - assessed by digital images at 6 weeks.

6.4 Secondary Objectives

Secondary objectives are:

- To assess time to complete healing
- To assess the safety and tolerability of the compared treatments.
- To assess the cost-effectiveness of the compared treatments.

7. TRIAL DESIGN

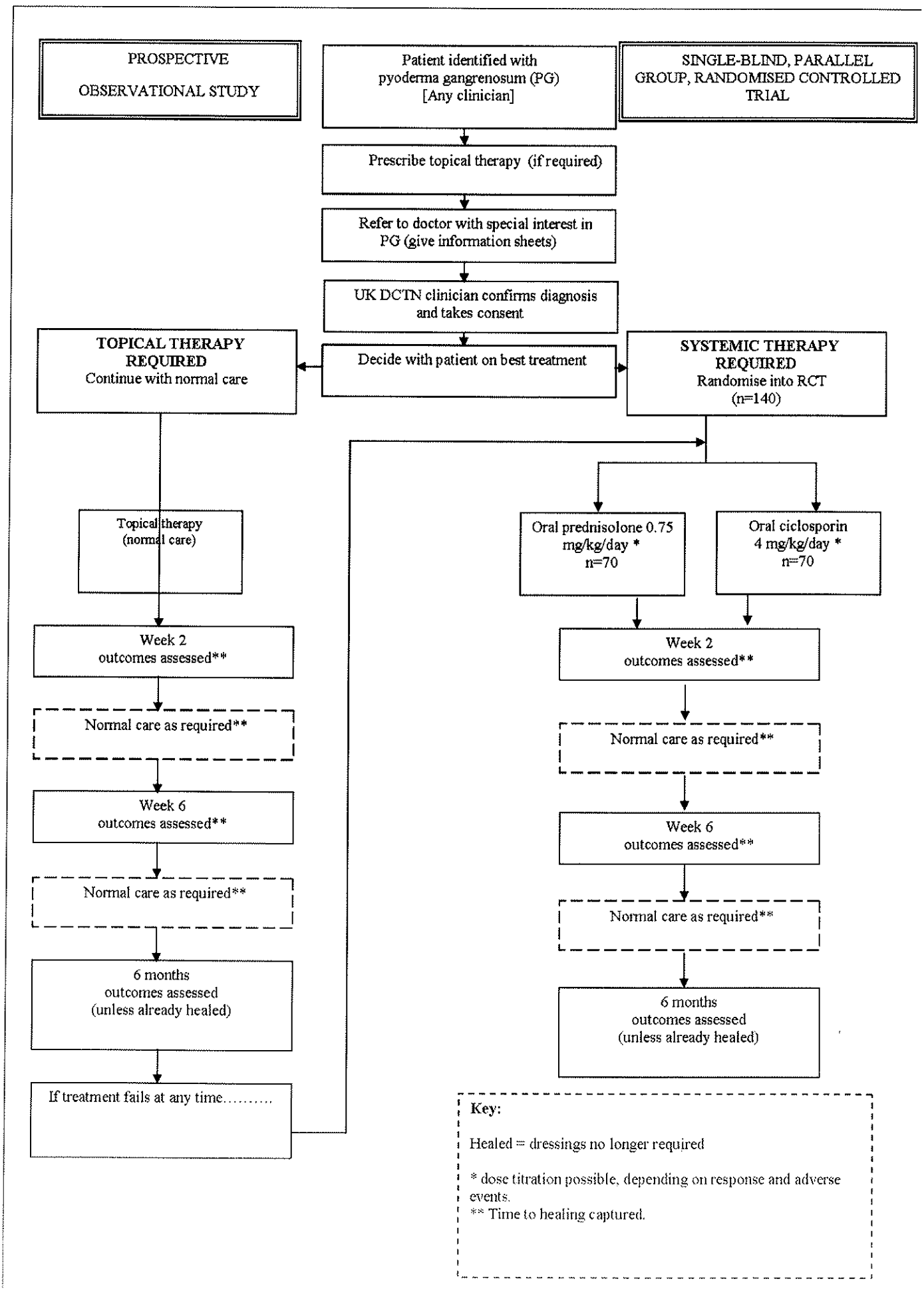
7.1 Trial Configuration

This is a multi-centre, parallel group, randomised controlled trial (see figure 1). The study is to be single blind for the primary outcome of speed of response at 6 weeks (digital images taken in clinic will be assessed centrally using specialist software). Because of logistic and methodological difficulties in blinding treatment allocation, both participants and treating physicians will be aware of treatment allocation.

Participants will be randomised to receive either oral prednisolone (0.75 mg/kg/day, up to a ceiling dose of 75 mg/day) or oral ciclosporin (4mg/kg/day, up to a ceiling dose of 400 mg/day). Participants for whom 1st line topical therapy is indicated will enter the observational study – only if this treatment fails will participants be invited to take part in the randomised trial. Sufficient numbers of patients in the observational study will give useful empirical clinical information and provide an indication of the effectiveness of topical therapy for milder cases of PG.

Participants will continue to be monitored until the lesion has healed, or for a maximum of 6 months (whichever is sooner). Consent will also be obtained for the research team to contact the participants after this time (or to access medical records), in order to capture details of future episodes of PG.

Figure 1 Flow diagram of study design


PROSPECTIVE
OBSERVATIONAL STUDY
Patient identified with pyoderma gangrenosum (PG) [Any clinician]
SINGLE-BLIND, PARALLEL GROUP, RANDOMISED CONTROLLED TRIAL
Prescribe topical therapy (if required)
Refer to doctor with special interest in PG (give information sheets)
UK DCTN clinician confirms diagnosis and takes consent
Decide with patient on best treatment
TOPICAL THERAPY REQUIRED
Continue with normal care
SYSTEMIC THERAPY REQUIRED
Randomise into RCT
(n=140)
Topical therapy (normal care)
Oral prednisolone 0.75 mg/kg/day *
n=70
Oral ciclosporin 4 mg/kg/day *
n=70
Week 2 outcomes assessed**
Normal care as required**
Week 6 outcomes assessed**
Normal care as required**
6 months outcomes assessed (unless already healed)
If treatment fails at any time.....
Week 2 outcomes assessed**
Normal care as required**
Week 6 outcomes assessed**
Normal care as required**
6 months outcomes assessed (unless already healed)
Key:
Healed = dressings no longer required
* dose titration possible, depending on response and adverse events.
** Time to healing captured.

7.2 Primary endpoint

- ***Velocity of healing.***

  This will be captured for a single target lesion per patient and measured using digital photography and VEV computerised planimetry (2). If multiple lesions are present, the target lesion should be the lesion that is most able to be photographed on a single plane (i.e. not around the curvature of a limb) for study will be the largest of those present. Digital images will be taken at baseline, 6 weeks and when the ulcer has healed (max 6 months). In addition, maximum longitudinal length and maximum perpendicular width will be measured in order to provide some measure of improvement in case of difficulties with the digital images. This will be converted to approximate area by the formula: length x width x 0.785, which approximates to an ellipse for the purpose of randomisation and analysis.

  This outcome has been chosen as the primary outcome measure as it is:

  1) unlikely to be compromised by the single-blind nature of the study

  2) should result in complete data for almost all participants

  3) does not require lengthy follow-up and

  4) previous work in patients with venous leg ulcers would suggest that velocity of healing is a good surrogate for subsequent healing (3).

7.3 Secondary endpoint

- **Time to healing** - assessed by participants (estimated to the nearest week) based on the time at which sterile dressings are no longer required for the wound. Healing will be confirmed using digital photography at the first opportunity. Information will be provided to participants with instructions on how to report healing of the ulcer. Lesions that remain unhealed after 6 months will be considered to be treatment failures.

  Time to healing is a more ***clinically relevant*** outcome than velocity of healing. It also gives some indication of duration of treatment, which therefore gives an indication of cumulative drug toxicity.

- **Global assessment of improvement (PG specific)** – as assessed by the clinician and the patient at 2 weeks, 6 weeks and at 6 months (or healed) (4). This will also be assessed on the digital images by an independent assessor.

- **Inflammation assessment scale** – combination scale including erythema, border elevation and exudate based on a scale reported by Foss et al (5). Assessed at baseline, 2 weeks, 6 weeks and when the ulcer has healed (max 6 months). Assessed by the clinician, patient and assessed on digital images.

- **Self-reported pain** - assessed daily in diaries for the first 6 weeks.
- Impact on **health-related quality of life** – assessed at baseline, 6 weeks and 6 months (or healed), using a dermatology specific tool 'Dermatology Life Quality Index' (6), and a general utility measure, the 'EQ-5D' (7).
- **Time to recurrence** in each treatment group at the end of the trial. A recurrence is defined as being a repeat episode of PG (at any site) that appears after the lesion has been confirmed as being healed by a physician (or nurse). Self-reported healing that has not been confirmed by a medical professional, and which subsequently recurs, will not be classed as a recurrence and handled as a continuation of the initial episode.
- **Number of treatment failures** – treatment failures are defined as being participants who withdraw (or are withdrawn) from their randomised treatment because of treatment intolerance or worsening of the PG, or those who continue to have any unhealed ulcers after 6 months of follow-up.
- **Adverse reactions to study medications** – adverse events that are classed as possibly, probably or definitely relating to the study medication, as per appendix 7.
- **Cost-effectiveness** of the compared treatments.

For the observational study, we will collect efficacy outcomes only. No safety or cost-effectiveness data will be collected.

7.4 Data collection schedule

This is a pragmatic trial that aims to reflect current practice as far as possible and study visits have been organised to fit in with normal care. It is anticipated that no additional visits will be required for research purposes other than an additional visit once the lesion has healed (in order to confirm the status of the lesion). Local investigators are recruiting into this trial on a voluntary basis and so every effort has been made to keep the schedule of visits and necessary paperwork as straight-forward as possible.

All participants will be seen at baseline, 2 weeks, 6 weeks and when the ulcer has healed (max 6 months). Any participant who is unable to make a study visit will be followed-up by telephone and postal questionnaire, although every effort will be made to obtain a digital image of the ulcer as close to the date of the study assessment visit as possible. In exceptional cases, a home visit may be arranged.

The point at which dressings are no longer required will be reported by the participants, following a standard procedure. Healing will be confirmed using clinical photography as soon as possible thereafter. Self-assessed pain will be recorded in a daily diary.

Standard tests and investigations will be conducted at the pre-recruitment/baseline visit and repeated at subsequent visits as clinically necessary. For participants randomised to ciclosporin, creatinine levels should be monitored per the guidance found in the summary of product characteristics (section 4.4). Non-study visits will be at the discretion of the treating physician and will follow standard practice for the individual hospital. Subsequent visits are likely to be at least monthly according to normal practice. Data collection at these visits will be limited to longitudinal length and perpendicular width measurements of the lesion; changes to the dose of the study medications; identification of adverse events.

If local support is available through the Comprehensive Local Research Network (or equivalent in Wales and Scotland), then local research nurses may assist with data collection, maintenance of site files and data entry. If a research nurse is not available, these activities will be conducted by the recruiting physician.

Table 1: Summary of data collection schedule at site

Procedures and data collection conducted at site	Week 0 (baseline)	Week 2 (± 1 week)	Week 6 (± 1 week)	Final visit (maximum 6 months ± 1 month)
Clinical diagnosis of PG confirmed (including biopsy if clinically indicated). If diagnostic uncertainty send digital image to panel of experts	X			
Obtain informed consent	X			
Standard tests conducted as per normal practice*	X	X	X	X
Ascertain the patient is eligible for the study	X			
Collect medical history and demographic data	X			
Take weight and blood pressure	X	X	X	X
Patient's assessment of target lesion	X	X	X	X
Patient's assessment of pain	X	X	X	X
Clinician's assessment of target lesion	X	X	X	X
Ulcer measurements (longitudinal length and perpendicular width)	X	X	X	X
Digital photograph of target lesion	X		X	X
Quality of Life Questionnaires	X		X	X
Issue prescription	X			
Adjust medication dosage as required		X	X	X
Collect adverse event data and report to co-ordinating centre according to guidelines		X	X	X
Collect health service resource use data	X	X	X	X
Case Report Forms transferred to co-ordinating centre	X	X	X	X
Document study medication usage		X	X	X

Notes:
In addition to the visits outlined above, participants will attend clinic as per normal care. The total number of clinic visits and clinical decision-making will be abstracted onto Case Report Forms following an examination of the clinical notes. This information will be used to inform the cost-effectiveness analysis.

* Urea electrolytes (inc creatinine), FBC, CRP, rheumatoid factor and autoantibodies, ANCA, serum immunoglobulins, urine pregnancy test for females, ulcer swab for bacteriology, glucose.

Ulcer healed (no longer requiring dressings) will be collected directly from the participants using diary report cards and telephone contact.

Recurrence data will be collected by accessing medical notes in order to establish whether the patient had a recurrence following their participation in the trial. The date of first recurrence will be captured.

7.5 Week 0: Baseline assessment

Patients that have been identified as having PG will be given information about the trial and referred to one of the recruiting clinicians on-site for confirmation of diagnosis and ongoing management. If necessary, patients may be prescribed topical therapy prior to referral to the recruiting physician or whilst considering participation into the study. This is most likely to be either clobetasol propionate (Dermovate®), or tacrolimus (Protopic® 0.1%, 0.03%), according to local practice.

The main aim of the baseline visit is to obtain informed consent, screen for eligibility, samples for diagnostic tests (if applicable and required for normal practice), record baseline general health state, severity of disease and other assessments and to start the patient on the study drugs. It is anticipated that the patients will have received participant information sheets when the referral was arranged, and have been given time to consider whether or not they wish to take part. However, PG is a painful, debilitating condition and some patients may choose not to delay treatment, in which case, patients may be randomised into the study on the same day. If a patient is found to have PG, but is unsuitable for systemic therapy, then consent will be sought to enter them into the prospective observational study. Data collection in the observational study will be limited to efficacy data only.

Procedures to be carried out at baseline:

- Discuss the study with the patient and answer further questions about the study.
- Obtain consent from the patient before proceeding with the study.
- Check participant meets all eligibility criteria.
- Take digital image of the lesion (using an index card, called a target plate, next to the lesion) – following a standard procedures for taking and storing the digital images.
  If diagnostic uncertainty – send image to expert panel and conduct a biopsy of the lesion.
- Take samples for full blood count, liver function tests, creatinine and urea. Collect sample for urine screen (sediment, protein and glucose). The results of these tests will not be analysed within the study, but they should be checked by the clinician in the normal way and any clinically significant findings reported in the medical notes and AE logs.
- Perform physical examination including blood pressure and weight.
- Obtain medical history, relevant concurrent medication and demographic data.
- Agree on target lesion with participant.
- Assess the target lesion, longitudinal length & perpendicular width, inflammation assessment.
- Ask participant to assess pain.
- Ask the participant to complete study questionnaires.

- Give study diary to participant and request they record pain, use of dressings, any medical problems and health service usage.
- Complete the prescription form.
- Complete CRF (case report form).
- Issue medical alert card to patient.

7.6 Week 2: Assessment of response and side-effects

This visit will take place in order to assess response to treatment and to adjust trial medication dosage as necessary. All study related procedures will be as per week 6, except that a digital image is not required and QOL data is not being collected.

7.7 Week 6: Assessment of primary outcome and side-effects

This visit is crucial for the collection of primary outcome data and should be at 6 weeks (± 1 week) post randomisation if at all possible.

Procedures to be carried out at week 6:

- Take samples for full blood count, liver function tests, creatinine and urea. Collect sample for urine screen (sediment, protein and glucose). The results of these tests will not be analysed within the study, but they should be checked by the clinician in the normal way and any clinically significant findings reported in the medical notes.
- Perform physical examination including blood pressure and weight.
- Check treatment adherence.
- Adjust treatment dose as required (up or down).
- Check adverse events.
- Assess the target lesion (including digital image, longitudinal length & perpendicular width, inflammation assessment, global improvement).
- Ask participant to assess response of target lesion and pain.
- Ask the participant to complete quality of life questionnaires
- Assess health services resource usage.
- Give new study diary to participant and request they record any medical problems, health service usage and use of dressings – RCT patients only.
- Complete CRF (case report form).

7.8 Subsequent visits

Further visits to clinic are at the discretion of the treating physician. Limited details relating to treatment response, safety and health service resource use will be captured on Case Report Forms and/or medical notes. A 'Change of Status' CRF will be completed if a participant withdraws from either the study medications or the study as a whole.

Participants will be asked to report to either the co-ordinating centre or to their treating clinician when they no longer require dressings. At this point they will be asked to attend the clinic for confirmation that the ulcer has healed and for a digital image to be taken. If it is not possible for the participant to attend clinic, participants will be asked to visit their GP for confirmation of healing. If neither is possible, self-reported healing will be used. If the ulcer has not healed by 6 months post-randomisation, participants will be seen and a final visit CRF will be completed (or in exceptional cases, a home visit may be arranged).

If the clinician and/or patient are not satisfied with treatment response at any time, participants will be withdrawn from treatment and offered an alternative treatment regimen. These withdrawals will be classed as treatment failures and will continue to be followed-up as appropriate.

7.9 Treatment and Relapses

Participants will be asked to advise the co-ordinating centre, and return to the investigator for treatment if they have another episode of PG. Consent will also be obtained in order to contact patients again at the end of the trial (or to check their medical records) in order to assess future recurrence rates.

8. RANDOMISATION AND BLINDING

Participants will be randomised to treatment allocation using a computer-generated pseudo-random list using permuted blocks of randomly varying size between 2 & 6, created using the ralloc Stata add-on. Randomisation will be stratified by lesion size (lesions $\geq 20cm^2$ versus lesions $<20cm^2$) and presence or absence of underlying systemic disease (e.g. inflammatory bowel disease). The randomisation sequence will be concealed until interventions are all assigned and recruitment, data collection, and data cleaning are complete.

Accessing the randomised code to inform treatment assignment will be flexible according to local needs This may include:

- Recruiting physician / designee (using telephone, text or web-based randomisation)

The decision to enrol a patient into the randomised study or the observational study will be made by the participant following discussion with the treating physician. Participants who fail to respond to their allocated treatment will be withdrawn from the study treatment and offered alternative treatment. If

participants are withdrawn from treatment, they will continue to be followed up if the participant is happy with this arrangement.

This is an assessor-blind study. The clinicians and participants will know their treatment allocation and blind assessment of the primary outcome (velocity of healing) will be achieved using digital images of the target lesion. These will be assessed by a blinded investigator, using patient number as the identifier.

All treatments will be provided and dispensed by the local hospital pharmacy, or via community pharmacists if dictated by local practice.

8.1 Maintenance of randomisation codes and procedures for breaking code

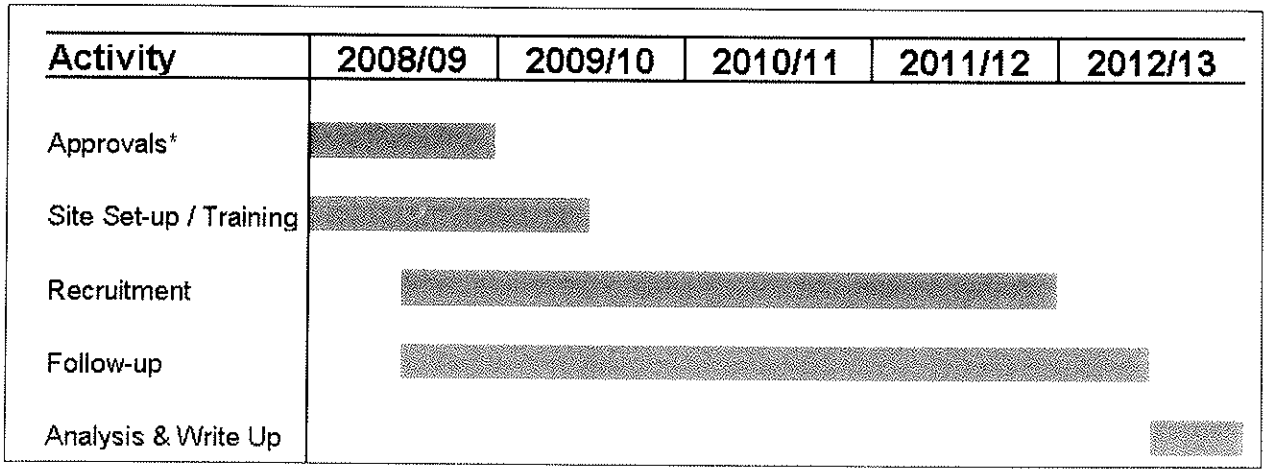
As both clinicians and patients will be aware of the treatment allocation throughout the study, no special measures are required in order to allow for breaking of treatment codes. Although the sequence of allocations must remain secret.

9. DURATION OF THE TRIAL

All participants will be enrolled in the study for six months, although long-term follow-up will continue in order to capture future relapses. The duration of treatment will differ between participants as treatment will be continued until remission is achieved.

This trial has funding in place to run from 1st September 2008 until 31st August 2013. It is anticipated that recruitment will take place over a 3-4 year period, starting once ethics and regulatory approvals are in place (anticipated start date April 2009).

Figure 1: Timescale for trial (starting Sept 2008)



9.1 End of the Trial

The end of the trial is defined as the last participant's last treatment visit (or after 6 months if treatment is ongoing).

10. SELECTION AND WITHDRAWAL OF PARTICIPANTS

10.1 Recruitment

Participants will be recruited in approximately fifty acute hospitals in the UK and Ireland. To recruit the expected 140 participants, each centre will need to recruit approximately 3-5 patients over the 3-4 year recruitment period. Centres may be approached in France, Italy, Germany and the Netherlands if recruitment is slower than anticipated.

Patients will be a mixture of inpatients and outpatients depending on local practice.

In the UK, recruitment will be through UK Dermatology Clinical Trials Network (UK DCTN). Over 70 dermatologists have already expressed an interest in recruiting into this trial, in a mixture of district general and teaching hospitals. In order to maximise recruitment into the trial, part of the recruitment strategy will be to encourage colleagues (both dermatologists and other relevant clinicians e.g. gastroenterologists, rheumatologists) to refer patients to the investigator for the trial. This will include presentations at regular meetings, prominent posters throughout the hospital, e-mail reminders and writing to previous patients.

The initial approach will be from a member of the patient's usual care team (which may include the investigator), and information about the trial will be on display in the relevant clinical areas.

The investigator or their nominee, e.g. from the research team or a member of the participant's usual care team, will inform the participant or their nominated representative, of all aspects pertaining to participation in the study. Patients will be given adequate opportunity, determined on an individual basis, to consider the study before deciding whether to take part. In some cases patients may prefer to enrol straight away so that treatment is not delayed, while others may prefer longer to consider the study and thus delay treatment for a short while.

Since pyoderma gangrenosum often recurs, we will also contact patients who have previously been treated at the hospital in order to inform them about the trial. All letters will come from the physician who treated them for their previous episode.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial, the participant information sheets, and consent forms. The consent forms and information sheets will not be available printed in other languages (unless recruitment is extended into Europe). It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw

at any time, but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that the data collected so far cannot be erased and that we will use the data in the final analyses.

10.2 Inclusion criteria

Patients with a presumed diagnosis of PG will be contacted about the study. The following inclusion criteria will apply.

- PG as diagnosed by the recruiting dermatologist. [An ulcerative lesion may have mixed aetiology, but provided the investigator has confidence that a clinical diagnosis of PG is appropriate then they are eligible. Other contributing factors and atypical features will be captured in the case report form].
- Must have a measurable ulceration (e.g. not pustular pyoderma gangrenosum)
- Age over 18 years.
- Able to provide written, informed consent.

Whilst a pragmatic approach has been taken to the diagnosis of PG, two steps will be implemented to ensure confidence in the recruiting physician's diagnosis.

1. Should the recruiting physician be in doubt as to the eligibility of a particular patient, a digital image will be sent to a panel of experts prior to randomisation; who will provide diagnostic advice.
2. In the case of diagnostic uncertainty, a biopsy will be taken as part of routine practice.

10.3 Exclusion criteria

10.3.1 Exclusions from both the RCT and observational study

Patients cannot participate in either the RCT or observational study if they have any of the following:

- Granulomatous PG – this condition is very rare and may respond differently to treatment.
- Ciclosporin or prednisolone or IVIG therapy in the previous month.
- Already participating in another clinical trial.

10.3.2 Exclusions from the randomised controlled trial arm of the study

Exclusions for the randomised controlled study (not the observational study) are as follows:

- Pregnant, lactating or at risk of pregnancy.
- Hypersensitivity to prednisolone or ciclosporin
- Biopsy consistent with a different diagnosis.
  Biopsies will be used to exclude alternative aetiologies (e.g. malignancy, granulomatous PG, arteritis) rather than to confirm the diagnosis of PG, since histology is supportive rather than pathognomic. Ideally, the biopsy will be a 1.5cm rectangular biopsy taken through the edge of the

ulcer and left to granulate and heal by secondary intention. Alternatively, 2 separate punch biopsies done at the edge of the ulcer and at the extending margin may be used. It is not normal practice to await histological confirmation before initiating therapy, so patients will be randomised prior to receiving histological results. If the histology indicates an alternative aetiology, the participant will be excluded at that time.

- Clinically significant renal impairment that would result in the investigator not normally treating with either study drug.
- Any pre-treatment investigations, the results of which would prompt the investigator not to use either study drug.
- A diagnosis of malignancy or pre-malignant disease where treatments might interfere with ongoing therapy or might cause harm (e.g. history of lymphoma, multiple lymphoma, leukaemia, cervical epithelial neoplasia – CIN, systemic cytotoxic therapy)
- The patient has a concurrent medical condition that means the investigator would not normally treat the patient with either of the study drugs (for example: a degree of hypertension that would not lead to using either of the study drugs, advanced heart failure, poorly-controlled diabetes, history of peptic ulcer, malignancy in previous years).
- Administration of a live vaccine (BCG, Measles, Mumps, Rubella, Yellow Fever, Oral Polio, Oral Typhoid) within the last 2 weeks
- The patient is currently taking Rosuvastatin (Crestor®) for the treatment of hypercholesterolaemia, since this is contra-indicated when taking Neoral® (ciclosporin).

10.4 Removal of participants from therapy or assessments

Participants shall be withdrawn from the trial if any of the following apply:

- If the patient is reluctant to continue with the trial.
- Clinician's discretion to withdraw patient from study (including severe secondary infection, pregnancy).
- Adverse effects from the medication (e.g. rising serum creatinine above 30% of baseline after 1 month despite dose reduction, diabetes due to the study intervention)
- do not meet the inclusion / exclusion criteria

A withdrawal Case Report Form will be completed for all participants withdrawing from the treatment or whole study.

Participants will be warned (in the participant information sheets and through discussion with their doctor) that the study medication should not be terminated abruptly as tapering of study drugs is required.

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw, the data collected to date cannot be erased and will still be used in the final analysis. Enrolled participants who are not yet randomised will be replaced (though keeping their trial ID), but participants who withdraw after randomisation will not be replaced and will be included in the intention to treat analysis. The only exception to this will be those for whom a biopsy is taken and the results suggest that the participant has something other than PG. Such participants will be withdrawn immediately and not included in the ITT analysis.

10.5 Informed consent

All participants will provide written informed consent. The Informed Consent Form will be signed and dated by the participant before they enter the trial. The Investigator will explain the details of the trial and provide a Participant Information Sheet (if the participant has not already received one), ensuring that the participant has had sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

Informed consent will be collected from each participant before they undergo any interventions related to the study. One copy of this will be kept by the participant, one will be kept by the Investigator, one will be sent to the co-ordinating centre and a fourth will be retained in the patient's hospital records. Normal clinical tests may be initiated prior to taking of signed consent if these constitute normal care.

Once randomised, patients will be contacted by the co-ordinating centre and willingness to continue in the trial will be confirmed.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended consent form which will be signed by the participant if they are within the 6-month intervention phase of the trial.

11. TRIAL TREATMENT REGIMEN

Participants enrolled in the RCT will receive either:

- Ciclosporin (Neoral) 4 mg/kg or
- Oral prednisolone 0.75 mg/kg

  A ceiling dose, based upon a 100 kg body weight, will be imposed on both drugs so the maximum advised starting daily dose will be 75 mg of prednisolone and 400 mg of cicosporin. The treating clinician may increase the starting dose, in line with the initial dose calculated below 100 kg body weight, if they feel it is appropriate and safe to do so. The rationale for the

ceiling dose is because using a mg/Kg formula would result in a very large initial dose being given to morbidly obese patients, and it is possible that such patients would be at increased risk of drug-related serious adverse events.

The dose of treatment can be altered (up & down) according to normal practice, although clinicians are encouraged not to alter the dose until week 2. Ciclosporin can be increased to a maximum of 5 mg/kg/day and prednisolone to a maximum of 1 mg/kg/day.

Different brands of ciclosporin are not interchangeable due to differences in their bio-availability.

If creatinine rises above 30% of baseline at more than one measurement, the study medication will be reduced by 25%-50%. If dosage reduction is not successful in reducing levels within one month, treatment should be discontinued.

If secondary infection is suspected, it will be treated appropriately with concomitant antibiotics and immunosuppressive therapy.

Participants enrolled in the observational study will receive which ever topical treatment is used in normal clinical care at the recruiting hospital (this is most likely to be clobetasol propionate (Dermovate®), or tacrolimus (Protopic® 0.1%, 0.03%)). Efficacy outcomes will be collected in the same way as for the randomised study.

11.1 Prohibited Concomitant Medications

For patients in the intervention phase of the trial, the administration of live virus vaccines (e.g. yellow fever) is not permitted. Patients will not be entered into the intervention phase if they are currently taking Rosuvastatin (Crestor®) since this is contra-indicated with Neoral® (ciclosporin) and clinicians will be advised not to start this drug if the participant is randomised to Neoral® (ciclosporin).

For those randomised to systemic therapy in the RCT, topical therapy (corticosteroids, calcineurin inhibitors and tacrolimus) will be prohibited. If topical therapy has already been prescribed whilst waiting to enter the study, the participant will be asked to stop using this treatment.

Participants should continue to take medications for other conditions as normal.

Caution with other concomitant medications

For an up to date full list of potential interactions see the Summary of Product Characteristics

For participants taking **prednisolone,** extra caution should be taken if concurrently taking any of the following medications:

- **Coumarin anticoagulants:** the efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy.
- **Salicylates:** The renal clearance of salicylates is increased by corticosteroids.
- **Hypoglycaemic agents:** the desired effects of hypoglycaemic agents (including insulin), anti-hypertensives and diuretics are antagonised by the corticosteroids.
- **Diuretics:** Hypokalaemic effects of acetazolamide, loop diuretics and thiazide diuretics are enhanced.
- **IUD for contraception:** increased risk of pregnancy.

For participants taking **ciclosporin,** extra caution should be taken if concurrently taking any of the following medications:

- **Statins:** the dose of the statin may need to be reduced to avoid increased risk of muscle toxicity.
- **Diclofenac:** reduce the dose of diclofenac by half.
- **Food interactions:** the concomitant intake of grapefruit juice has been reported to increase the bioavailability of ciclosporin.
- **Drugs that decrease ciclosporin levels:** barbiturates, carbamazepine, oxcarbazepine, phenytoin, rifampicin, octreotide, orlistat, hypericum perforatum (St John's Wort), ticlopidine, sulfinpyrazone, terbinafine, bosentan.
- **Drugs that increase ciclosporin levels:** macrolide antibiotics (e.g. erythromycin and clarithromycin), ketoconazole, fluconazole, itraconazole, voriconazole; diltiazem, nicardipine, verapamil, metoclopramide, oral contraceptives; danazol; methylprednisolone (high dose); allopurinol; amiodarone; ursodeoxychloric acid; protease inhibitors, imatinib; colcichine.
- **Potassium sparing drugs:** caution is required if patients are taking potassium-sparing drugs (e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists) due to the increased risk of hyperkalaemia, especially in patients with renal dysfunction.
- **Digoxin:** caution is required if patients are taking digoxin, since severe digitalis toxicity has been seen within days of starting ciclosporin in several patients taking digoxin.

Consideration of monitoring blood levels is advised where these concomitant medications are considered to increase the risk of toxicity, e.g. erythromycin.

In addition to this specific list, investigators will be advised to ensure they follow the advice in the current British National Formulary concerning interactions.

11.2 Adherence

This is a pragmatic study that seeks to reflect current practice as far as possible (regardless of whether or not the drugs have been taken appropriately). PG is a painful and debilitating condition, making it more likely that participants will comply with treatment. In addition, participants will be strongly advised not to stop their treatments suddenly, as the dose must be tapered prior to stopping altogether.

Participants will be asked to assess how well they adhered to the study drug at week 6 and at 6 months (or time of healing).

11.3 Packaging

Participants will be prescribed study medication from standard pharmacy supplies and the participant will not be blinded to treatment allocation, so no special packaging or labelling will be used.

11.4 Storage, dispensing and return

The study drugs will be stored as per the manufacturers instructions in the study centre pharmacies. Participants will be instructed to store medication not above 25°C.

Participants will be instructed to dispose of unused medication according to local hospital policy.

11.5 Accountability for drugs

If drugs are dispensed through the local Clinical Trials Pharmacist, detailed dispensing records will be kept by each dispensing pharmacy including:

- Patient's name
- Dose and duration
- Batch number, expiry date, manufacturer, brand

If local practice dictates that prescriptions are dispensed by a community pharmacist or normal hospital pharmacy, normal prescription practice will be followed. Details of the drug and total dose will be recorded in the patient's hospital notes.

11.6 Management of study drug overdose

Prednisolone

Treatment is unlikely to be needed; serum electrolytes should be monitored.

Ciclosporin

No experience of acute overdosage with NEORAL is available. Symptomatic treatment and general supportive measures should be followed in all cases of overdosage. Forced emesis could be of value within the first few hours after intake. Signs of nephrotoxicity might occur which should be expected to resolve following drug withdrawal. Ciclosporin is not dialysable to any great extent nor is it well cleared by charcoal haemoperfusion. Hypertension and convulsions have been reported in some patients receiving ciclosporin therapy at doses above the recommended range and in others with high trough blood levels of ciclosporin. This might therefore, be expected as a feature of overdosage.

11.7 Criteria for terminating trial

The following may result in the trial being terminated:

- Informal interim analysis conducted by the DMC suggests overwhelming evidence of effectiveness / ineffectiveness.
- Major safety concerns.
- Insurmountable issues with trial conduct (e.g. poor recruitment, loss of resources).
- A regulatory decision, a change in opinion of the REC or sponsor withdrawal.

Recruitment at a particular study site may be stopped for reasons of low recruitment or compliance issues.

12. STATISTICS

12.1 Principles governing the statistical methods

The primary analysis will be according to the intention to treat principle, and will adjust for known prognostic baseline co-variates. All analyses will be fully specified in a Statistical Analysis Plan, to be agreed before unblinding the data by the Trial Steering Committee. The influence of missing data will be examined using multiple imputation techniques. There are no formal planned interim analyses, but progress reports on all data issues will be presented to a Data Monitoring Committee, who will agree their charter at their first meeting.

12.2 Sample size

One hundred and forty patients in total (randomised 1:1 to systemic prednisolone or systemic ciclosporin will give the study at least 80% power at a 5% level of significance using a two sided two sample t-test to

detect a difference in means of 0.5 standard deviations of the primary outcome of velocity of healing at 6 weeks. The velocity of healing at six weeks is defined as the percentage change in surface area (measured by planimetry using digital photographs) over baseline of the target lesion. This sample size allows for an approximate 10% loss to follow up at 6 weeks. These calculations were performed using Nquery 6.0.2 on Windows XP.

12.3 Other statistical issues

We will build a prognostic model using baseline covariates on the primary outcome of velocity of healing (and in addition supporting models looking at time to healing and also healed by stated time milestones e.g. 6 months after treatment started). These will be regression models appropriate to the distribution of the outcome (e.g. linear models [velocity of healing], Cox proportional hazards survival models [time to healing], and logistic regression models [proportion healed at a stated time]). We will also consider exploratory regression tree analysis (CART) to identify more complex interactions between these baseline factors in identifying subsets of subjects who respond well or are resistant to treatments.

12.4 Cost-effectiveness analysis

Costs of the compared treatments will be assessed from the perspective of the health service. Cost-effectiveness will be presented as the cost per healed ulcer at 6 months.

Health related quality of life will be estimated from responses to the Dermatology Life Quality Index. Quality adjusted life years will be assessed from responses to the EQ-5D questionnaire, and the incremental cost per quality adjusted life years gained will be presented for the compared treatments. Health state utilities will be calculated using UK population tariffs. Estimates of resource utilisation (from medical records and patient diaries) will be combined with unit costs, to derive total costs. Unit costs will be based on study specific estimates and data from standard sources. Point estimates of mean incremental costs, QALYs, cost per QALY and cost per resolved episode at 6 months will be reported. Confidence intervals will be generated on estimates by bootstrapping.

To inform these analyses the following resource items will be recorded (all are PG-specific): in-patient stays, out-patient attendances, primary care appointments (at surgery), home visits by GP, district nurse visits, PG-related treatment costs. Detailed methods for the cost-effectiveness analysis will be prepared as part of the analysis plan.

12.5 Definitions of population analysed

This will be covered in detail in the Statistical Analysis Plan but the primary analysis will be based on the intent to treat population. Any participants found to have been misdiagnosed as having PG following receipt of biopsy results will be excluded from the analysis and will not be included in the intent to treat population.

13. ADVERSE EVENTS

13.1 Collection of Adverse Event data

This trial is using licensed drugs (prednisolone and ciclosporin) for which the side-effect profiles are well established. Only adverse events that are related or likely to be related to the study drug will be collected, i.e. adverse reactions. The known side effects of prednisolone and ciclosporin are listed in the summary of product characteristics, and as per appendix 7 of this protocol.

Worsening of the PG will NOT be classed as an AE as this will be captured by the efficacy outcomes.

13.2 Definitions

An adverse reaction (AR) is defined as:

- any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject

For the purpose of this study an adverse reaction includes:

- any study drug related event as listed in appendix 7
- any condition detected or diagnosed after medicinal product has been administered and has a possible, probable or definite causal relationship with the study drug.

An AR does not include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that leads to the procedure is an AE.

2. pre-existing disease or conditions present or detected at the start of the study that did not worsen.

3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

4. disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.

5. overdose of concurrent medication without any signs or symptoms.

A ***Serious Adverse Event*** (SAE) is any adverse event as defined by the protocol that occurs, having received the study medication that results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalisation or prolongation of existing hospitalisation
- A disability / incapacity
- A congenital anomaly in the offspring of a participant

All adverse events will be assessed for seriousness by the treating physician. Those events that are considered to be serious will also be assessed for expectedness and causality.

Hospitalisations resulting from a worsening of the PG will not be classed as SAEs, but will be captured as part of the economic evaluation of the trial.

Causality will be assigned as: not related or improbable, possible, probable or definite.

Medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate.

A ***Suspected Unexpected Serious Adverse Reaction*** (SUSAR) is a serious adverse event that is either sudden in its onset, unexpected in its severity and seriousness or not a known side effect of the study medication *and* related or suspected to be related to the study medication. SUSARs require expedited reporting as per the clinical trials regulations.

All serious adverse events that fall or are suspected to fall within these criteria shall be treated as a SUSAR until deemed otherwise.

13.1.1 Serious Adverse Events (Chief Investigator responsibilities)

For serious adverse events, the Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the study drug
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action
- If the event is deemed a SUSAR, shall, within seven days, complete the CIOMS form and send to the competent authority.
- Shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event

- Shall, within a further eight days send any follow-up information and reports to the competent authority and REC.
- Make any amendments as required to the study protocol and inform the ethics and regulatory authorities as required

13.2 Reporting of adverse events

All serious adverse events will be recorded and monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause. The treating physician shall determine seriousness and causality, and report any serious adverse reactions to the co-ordinating centre / Chief Investigator immediately.

In the event of a pregnancy occurring in a trial participant monitoring shall occur during the pregnancy and after delivery to ascertain any trial related adverse events in the mother or the offspring.

All serious adverse events will be recorded and reported to the competent authority and REC as part of the annual reports. SUSARs will be reported within the statutory timeframes to the competent authority and REC. The Chief Investigator shall be responsible for all adverse event reporting.

The DMC will review SAEs and SUSARs in line with the DMC charter.

14. ETHICAL AND REGULATORY ASPECTS

14.1 Ethics Committee and Regulatory Approvals

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the competent authority(s), Research Ethics Committee (REC), and the respective Research & Development (R&D) department within a Trust. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and Lead CLRN (via CSP). A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the competent authority, R&D and REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the Department of Health Research Governance Framework for Health and Social care, 2005.

14.2 Informed Consent and Participant Information

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant or other legally authorised representative shall both sign and date the Informed Consent Form before the person can participate in the study.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

14.3 Records

14.3.1 Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation, for use on CRFs other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth.

The investigator will also keep a screening log with details of all patients screened for the trial (including those who were then randomised) with their name, date of birth, local hospital number or NHS number and Trial number.

CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Site Responsibility Delegation Log.'

All paper forms shall be filled in using a ballpoint pen. Errors shall be lined out but not obliterated and the correction inserted, initialled and dated.

The recruiting clinician shall sign a declaration ensuring accuracy of data recorded in the CRF.

14.3.2 Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. The CRF will serve as its own source for some data, for example the inflammation assessment scale (see source document verification form). Only trial staff as listed on the Site Responsibility Delegation Log and Co-ordinating centre delegation log shall have access to trial documentation other than the regulatory requirements listed below.

14.3.3 Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, sponsor's designee and inspection by relevant regulatory authorities (e.g., MHRA, IMB, EMEA).

14.4 Data Protection

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords. Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media.

15. QUALITY ASSURANCE & AUDIT

15.1 Insurance and Indemnity

In the UK, Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures. In Ireland, Insurance and indemnity for trial participants and trial staff is either covered by the Clinical Indemnity Scheme or the relevant local Trust policy.

15.2 Risk Assessment

There is little additional risk or benefit to the individual participant by entering this study. Both study drugs are standard treatments for PG and the risks associated with both treatments are well documented. All participants in the study will receive an active drug (there is no placebo arm). Therefore, there is no additional risk to participants to that of normal clinical care. The results of this study will help inform clinical treatment decisions that will benefit society as a whole.

15.3 Trial Conduct

This trial will be conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice E6 (ICH-GCP) and the applicable regulatory requirements. The protocol will undergo peer review by the Nottingham Clinical Trial Unit to ensure compliance with GCP. All study documents study procedures will be prepared to ensure compliance with GCP.

The Trial Manager will ensure that all study procedures are followed and any deviations documented and investigated and will put in place measures to avoid a repeat.

One or more study training days will be arranged for training recruiting centres. These training days will cover all relevant aspects of GCP and all study procedures and SOPs. In addition, on-line training will be available, or the trial manager will visit sites where necessary to conduct further training and to provide assistance.

The trial will be managed from the central co-ordinating centre at the Nottingham Clinical Trials Unit. The day-to-day co-ordination of the trial will be the responsibility of the Trial Manager, (supported by the Trial Administrator).

The trial will be overseen by a trial steering committee (TSC), which will meet approximately once a year, depending on the progress of the trial. This will include an independent chair and two other independent members, along with the Chief Investigator, Lead Clinician, Programme Manager and Trial Manager. The Trial Management group (TMG) will comprise the trial manager, statistician, lead clinician, a recruiting clinician, programme manager and chief investigator. They will meet regularly (face-to-face or by conference call to facilitate the smooth running of the study) and make day-to-day decisions. Other members of the study team will be invited to the TMG meetings as appropriate.

A Data Monitoring Committee (DMC) will also be convened for this study. All members will be independent of the applicants and study team, although it is expected that the Trial Manager, plus 1-2 other member of the TMG will attend the meetings in order to inform the DMC about trial progress. This

committee will meet at least once a year and will oversee all ethical and safety issues in accordance with current regulations and MRC guidelines for DMCs.

15.4 Trial Data

Central monitoring of the data will be carried out by the Trial Manager and the Data Manager as the data are received at the co-ordinating centre and entered onto the study database.

Trial data at sites will be primarily monitored under existing governance arrangements by the particular trusts. However, the trial manager (or UK CLRN research staff) will monitor data where there is a specific need, or if problems are found with data from a particular centre.

Monitoring visits will cover as a minimum:

- Primary outcome variable and major secondary outcome variables
- Adverse events
- Correct treatment assignment
- Informed consent
- Completion/withdrawal

Monitoring visits will be followed by a monitoring report, summarising the findings during the visit and recommending remedial actions as necessary.

An audit of the Trial Master File for inclusion of essential documents as defined by Good Clinical Practice will be conducted annually.

15.5 Record Retention and Archiving

In compliance with the ICH/GCP guidelines, regulations and in accordance with Nottingham University Hospitals NHS Trust policy, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File, trial documents and database will be held by the Chief Investigator on behalf of the Sponsor. They shall be finally archived at secure archive facilities either at Nottingham University Hospitals NHS Trust or using off-site archiving facilities.

15.6 Discontinuation of the Trial by the Sponsor

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

15.7 Statement of Confidentiality

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.
Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, Nottingham University Hospitals NHS Trust representatives, the REC, local R&D Departments and the regulatory authorities.

16. PUBLICATION AND DISSEMINATION POLICY

The results of the study will be submitted for publication in a peer review journal as soon as possible after analysis. The authorship will be in line with the UK DCTN publication policy. A writing team will be convened who will take on the responsibility for writing the paper and the author will be the STOP GAP Study Team. All Principal and co-investigators will be named in the acknowledgements, detailing their role in the study. Participants will not be identified in any publications.

17. USER AND PUBLIC INVOLVEMENT

Service users have commented on the design and conduct of this study as part of our initial pilot work. Two structured interviews and a focus group discussion (involving three patients) have been conducted. The results of these discussions were used to inform the choice of study design / treatments, outcomes measures (outcome measures were amended following these discussions) and comments were made as to the clarity of the participant information sheets.

Patients who were involved in the focus groups, who were happy to be contacted again, will be invited to act as a patient *representative* for the trial and to contribute to steering committee meetings where appropriate.

18. STUDY FINANCES

18.1 Funding source

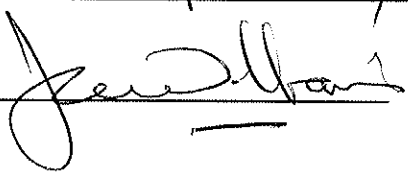
This study is funded by the National Institute for Health Research (NIHR) as part of an NIHR programme grant award to the Nottingham University Hospitals NHS Trust.

18.2 Participant stipends and payments

Participants will not be paid to participate in the trial. However, an allowance will be offered following the visits at baseline, week 6 and when returning to clinic in order to report time to healing (or 6 month visit if ulcer does not heal). This allowance is intended to cover expenses / inconvenience for the participants and will be paid in the form of a gift voucher.

19. SIGNATURE PAGES

Chief Investigator: (name) PROF. HYWEL WILLIAMS

Signature: 

Date: 5/9/11

I confirm I have read and understood this protocol and I agree to conduct the study in accordance with the protocol.

Principal Investigator: _____

Centre name: _____

Signature: _____

Date: _____

20. REFERENCES

1 Reichrath J, Bens G, Bonowitz A. Treatment recommendations for Pyoderma Gangrenosum: An evidence-based review of the literature based on more than 350 patients. *J Am Acad Dermatol* 2005; **53**: 273-83.

2 Wunderlich, RP, Peters EJG, Armstrong DG, Lavery LA Reliability of digital videometry and acetate tracing inmeasuring the surface area of cutaneous wounds. Diabetes Research and Clinical Practice 29 (2000) 87-92.

3 Kantor, J. Margolis, DJ A multi-centre study of percentage change in venous leg ulcer area as a prognostic index of healing at 24 weeks. Br J Dermatol. 2000 May;142(5):960-4.

4 CE Foss, AR Clark, R Inabinet, F Camacho, JL Jorizzo. An open-label pilot study of alefacept for the treatment of pyoderma gangrenosum. JEADV 2008, 22, 943 - 949

5 CE Foss, AR Clark, R Inabinet, F Camacho, JL Jorizzo. An open-label pilot study of alefacept for the treatment of pyoderma gangrenosum. JEADV 2008, 22, 943 - 949

6 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): A simple practical measure for routine clinical use. Clinical and Experimental Dermatology 1994: 210 - 216

7 EQ-5D, Euroqol.org

21. APPENDICES

21.1 APPENDIX 1

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date: Score:

Name: Diagnosis:

Address:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant

Please check you have answered EVERY question. Thank you.

21.2 APPENDIX 2

Health Questionnaire

English version for the UK (validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

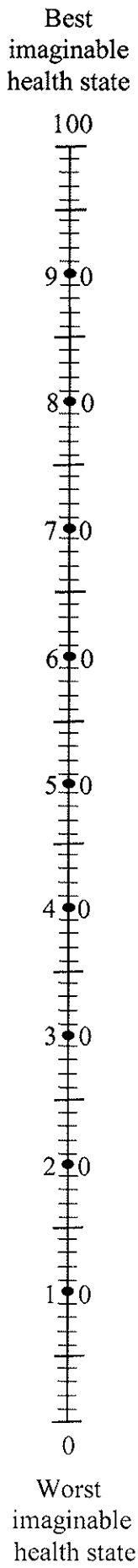
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Investigator Global Assessment of Efficacy

Apply the following scores to rate overall efficacy:

0	completely clear: except for possible residual hyperpigmentation
1	almost clear: very significant clearance (about 90%); however, patchy remnants of dusky erythema and/or very small ulceration
2	marked improvement: significant improvement (about 75%); however, a small amount of disease remaining (i.e. remaining ulcers, although have decreased in size, minimal erythema and/or barely perceptible border elevation)
3	moderate improvement: intermediate between slight and marked; representing about 50% improvement
4	slight improvement: some improvement (about 25%); however, significant disease remaining (i.e. remaining ulcers with only minor decrease in size, erythema or border elevation)
5	no change from baseline
6	worse

Patient's Global Assessment

The following scores were used to rate overall efficacy:

0 = Completely clear (skin colour may have changed)

1 = Almost clear (about 90% improvement)

2 = Marked improvement (about 75% improvement)

3 = Moderate improvement (about 50% improvement)

4 = Slight improvement (about 25% improvement)

5 = No change

6 = Worse

21.5 APPENDIX 5

Investigator Inflammation Assessment

Severity rating score	Description
Erythema	
• None (0)	• No erythema
• Slight (1)	• Mild pink colour
• Moderate (2)	• Moderate pink colour
• Severe (3)	• Reddish colour
• Very severe (4)	• Dark red or violaceous
Border elevation	
• None (0)	• Border is flat with ulcer and surrounding skin, no elevation
• Slight (1)	• Slight elevation of border above ulceration and surrounding skin
• Moderate (2)	• Noticeable elevation of border above ulceration and surrounding skin
• Severe (3)	• Significant elevation of border above ulceration and surrounding skin
• Very severe (4)	• Border rolled high above ulceration and surrounding skin
Exudate	
• None (0)	• Wound is dry
• Slight (1)	• Spotting of clear fluid
• Moderate (2)	• Moderate amount of discharge, partially discoloured
• Severe (3)	• Heavy, discoloured discharge
• Very Severe (4)	• Copious, offensive or blood stained discharge

21.6 APPENDIX 6

Summary of reasoning behind design decisions

Should this be an equivalence or a superiority trial?

It is our opinion that this should be a superiority trial for the following reasons:

- ◊ Given that ciclosporin is considerably more expensive than prednisolone, it would need to be considerably better than prednisolone in order to warrant a change in clinical practice.
- ◊ No previous trials have been published in this area, so this decision is based on clinical judgement and evidence from case series. Nevertheless, there is an impression that ciclosporin may gain control more quickly than oral prednisolone and have a different side-effect profile that may make it more suitable for long-term therapy.
- ◊ With a rare condition such as PG, this is also a pragmatic decision. An equivalence trial would require considerably more patients and would probably be beyond the scope of the UK DCTN (and funders).

Should digital images be used to capture the primary outcomes or simple planimetry?

Results of our pilot work suggest that using digital images if both feasible and practical, and a standard protocol for taking the images has now been prepared. Planimetry was rejected during the trial development as it was felt to be a biohazard, and that it would be difficult to store and transport the tracings (particularly with fears of MRSA).

In addition, the extra quality of data available from a digitally stored image may be useful in assessing ***global*** improvement of the ulcer remotely.

Since this trial is to be a single-blind study, it is important that outcomes can be assessed objectively by a blinded observer. Such a principle could only be followed by using digital images.

21.7 APPENDIX 7

0	**No side effects:**
1	**Blood and the lymphatic system disorders:**
1a	Anaemia
1b	Thrombocytopenia
1c	Leucocytosis
1d	Other (please state)
2	**Endocrine disorders:**
2a	Menstrual disturbances
2b	Gynaecomastia
2c	Cushings syndrome
2d	Hirsutism
2e	Diabetes
2f	Other (please state)
3	**Metabolism and nutrition disorders:**
3a	Hyperlipidaemia
3b	Hyperuricaemia
3c	Hyperkalaemia
3d	Hypomagnesaemia
3e	Hyperglycaemia
3f	Alcohol intolerance
3g	Other (please state)
4	**Nervous system disorder:**
4a	Tremor
4b	Headache
4c	Paraethesia
4d	Euphoria
4e	Mood swings
4f	Depression
4g	Personality changes
4h	Insomnia
4i	Psychosis
4j	Seizures
4k	Vertigo
4l	Other (please state)
5	**Gastrointestinal disorders:**
5a	Anorexia
5b	Nausea
5c	Vomiting
5d	Abdominal pain
5e	Diarrhoea
5f	Gingival hyperplasia
5g	Dyspepsia
5h	Peptic ulceration
5i	Abdominal distension
5j	Oesophageal ulceration
5k	Candidiasis
5l	Pancreatitis
5m	Perforation of bowel
5n	GI blood loss
5o	Other (please state)
6	**Cardiovascular disorders:**
6a	Hypertension
6b	Hypotension
6c	Congestive cardiac failure
6d	Oedema
6e	Other (please state)

7	**Hepato-bilary disorders:**
7a	Hepatic dysfunction
7b	Other (please state)
8	**Skin and subcutaneous tissue disorders:**
8a	Hypertrichosis
8b	Allergic rashes
8c	Bruising, petechiae and ecchymosis
8d	Skin atrophy
8e	Telangiectasia
8f	Acne
8g	Burning sensation
8h	Pruritus
8i	Erythema
8j	Facial flushing
8k	Folliculitis
8l	Other (please state)
9	**Musculoskeletal, connective tissue and bone disorders:**
9a	Muscle cramps
9b	Myalgia
9c	Myopathy
9d	Osteoporosis
9e	Avascular osteonecrosis
9f	Arthralgia
9g	Arthritis
9h	Tendon rupture
9i	Other (please state)
10	**Renal and urinary disorders**
10a	Renal dysfunction
10b	Other (please state)
11	**General disorders:**
11a	Serious infection – requiring hospitalisation or parenteral antibiotic
11b	Other infection
11c	Thrombo-embolism
11d	Fatigue
11e	Weight increase
11f	Cancer (please state)
11g	Other (please state)
12	**Allergy**
12a	Anaphylactic reaction
12b	Allergic reactions (not rashes)
12c	Rhinitis
12d	Other (please state)
13	**Ophthalmic**
13a	Increased intra-ocular pressure
13b	Glaucoma
13c	Papilloedema
13d	Cataracts
13e	Corneal or scleral thinning
13f	Exophthalmos
14	**Death**
15	**Other side-effects:**
	Please list