The **B**u**l**lous Pemph**i**goid **S**teroids and **Te**t**r**acyclines **(BLISTER)** Study

A randomised controlled trial to compare the safety and effectiveness of doxycycline (200 mg/day) with prednisolone (0.5 mg/kg/day) for initial treatment of bullous pemphigoid

Protocol

(UK version)

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2. ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
BP	Bullous Pemphigoid
CI	Chief Investigator overall
CRF	Case Report Form
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
EMEA	European Agency for the Evaluation of Medicinal Products
EOT	End of Trial
GCP	Good Clinical Practice
ICF	Informed Consent Form
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
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

3. SYNOPSIS

Title	A randomised controlled trial to compare the safety and effectiveness of doxycycline (200 mg/day) with prednisolone (0.5 mg/kg/day) for initial treatment of bullous pemphigoid.
Acronym	The BLISTER Study
Short title	The Bullous Pemphigoid Steroids and Tetracyclines Study
Chief Investigator	Professor Hywel Williams
Objectives	Primary • To assess whether doxycycline can be considered as non-inferior to prednisolone in effectiveness for the treatment of bullous pemphigoid. • To assess the safety of doxycycline compared with the prednisolone for the treatment of bullous pemphigoid. Secondary • To assess the cost-effectiveness of the two treatments.
Trial Design	Prospective, 2-arm, single-blind, parallel group, multi-centre randomised controlled trial.
Setting	Approximately forty-five hospitals in the UK and five hospitals in Germany and the Netherlands.
Number of participants	A total of two-hundred and fifty six participants will be recruited to the study (approximately 210 in the UK).
Main eligibility criteria	Main Inclusion Criteria: • At least eighteen years old. • Clinical features consistent with bullous pemphigoid. • A positive direct **or** indirect immuno-fluorescence. • At least three significant blisters at two or more body sites that have appeared in the week prior to study enrolment. • Free of blisters and any treatment for bullous pemphigoid for at least one year. Main Exclusion Criteria: • Any previous systemic medications for the treatment of the current episode of bullous pemphigoid. • Allergy to tetracyclines.

Study interventions	At baseline (week 0), participants will be randomised to receive either prednisolone (0.5 mg//kg/day) or doxycycline (200mg/day) for 6 weeks. From the 6 week visit onwards, the clinician will adjust the dosage to meet the clinical needs of the participant.
Duration of study	Recruitment will take place from January 2009 until December 2011. Last participant last visit will be December 2012. Each participant will be in the study for a total of 1 year.
Randomisation and blinding	Randomisation will be based on a computer generated pseudo-random code using random permuted blocks of randomly varying size. Participants will be allocated with equal probability to the doxycycline and prednisolone treatment arms. The investigator (but not the participant) will be blinded to treatment allocation for the initial treatment phase (week 0-6) until the results of the primary efficacy outcome measurement are recorded in the randomisation database. The remainder of the study (weeks 7-52) will be un-blinded to allow the investigator to adjust the study medication.
Outcome measures	Primary: Differences in the two treatment arms in the: • proportion of participants classed as treatment success (5 or less significant blisters present on examination) at 6 weeks. • number of reported grade 3, 4 and 5 (mortality) adverse events for one year. Secondary Differences in the two treatment arms in the: • proportion of participants classed as treatment success (5 or less significant blisters present on examination at 6 weeks) **and** are alive at one year. • proportion of participants classed as treatment success (5 or less significant blisters present on examination at 6 weeks) after 3 and 12 months of treatment. • proportion of participants who have a further episode of bullous pemphigoid during their participation in the study after previously being classed as a treatment success. • number of reported grade 1 and 2 adverse events for one year following the start of study treatment. • quality of life. • cost-effectiveness. Tertiary Differences in the two treatment arms in the: • proportion of participants who, on examination at 6 weeks, are completely blister free • proportion of participants who are alive 1 year after the start of study treatment. • proportion of participants in each treatment arm who, on examination at 3 weeks, are classed as treatment success (5 or less significant blisters present). • Difference in the amount of potent and super-potent topical corticosteroids used.

4. STUDY BACKGROUND AND RATIONALE

4.1. Background

Bullous pemphigoid (BP) is the most common of the autoimmune blistering skin diseases in the Western Europe. Estimates of incidence vary, but a recent audit of the Oxfordshire region (2001-4) showed the annual incidence of bullous pemphigoid in Oxfordshire to be 33.4 cases per million per year. One study in the Grampian region of Scotland showed an incidence rate of fourteen cases per million per year (1).

BP is a serious condition with a significant associated morbidity and mortality rate. Widespread tense and haemorrhagic blisters, skin erosions and severe itching cause patients a great deal of distress and pain. It occurs mainly in the elderly. The mortality rate in treated patients is estimated to range from 20% - 40% at one year. Patients are often admitted to hospital for initial treatment; estimates of admission rates vary, but they are generally high (up to 100%) thus representing a significant cost to the NHS.

A Cochrane systematic review (2) addressed the treatment of bullous pemphigoid and highlighted the lack of the evidence informing our current treatment and the UK guidelines (3). However, the severity of symptoms and lesions in bullous pemphigoid make treatment mandatory (usually with oral corticosteroids) and frequent hospital visits are needed for dose adjustment. It is thought that in this susceptible elderly population, this corticosteroid treatment contributes to the high mortality rate. This is due, at least in part, to the significant toxicity associated with the use of these drugs, such as hypertension, diabetes, infections and osteoporosis. Management of these conditions can be difficult and their treatment represents a significant burden to the NHS. Therefore, the avoidance of systemic corticosteroids in this vulnerable group of patients is highly desirable and a safer, effective, low cost alternative is needed.

There is some evidence that tetracyclines may be effective in treating bullous pemphigoid. Tetracyclines are cheap and readily available broad-spectrum antibiotics which have other non-antibiotic properties. In bullous pemphigoid, they are thought to work by decreasing the complement-mediated inflammatory response at the basement membrane zone by suppressing neutrophil chemotaxis and mediators of the inflammatory response.

The Cochrane systematic review (2) commented that “Combination treatment with tetracycline and nicotinamide may be useful; this needs further validation.” The review showed that the only published randomised controlled trial (RCT) to investigate tetracycline was small (20 patients) (4). It compared tetracycline (& nicotinamide) with prednisone and showed that tetracycline (& nicotinamide) may be effective in treating bullous pemphigoid, although the results were not statistically significant. There was one complete responder, and five partial responders in the steroid group (n=6), compared with five complete responders, five partial responders, one non responder, and one disease progression (n=12). Two participants were unavailable for follow up. The prednisone group had more severe adverse effects (including a death due to sepsis) and disease recurrence. Most of the adverse effects in the tetracycline (& nicotinamide) group were mild.

Several small open studies looking at tetracycline have also demonstrated the effectiveness of tetracycline for bullous pemphigoid. In the first study, four participants with

bullous pemphigoid were treated with tetracycline hydrochloride and nicotinamide and all showed an excellent clinical response with no side-effects (5). Similar results were found in a second study of seven participants with BP, where tetracycline combined with nicotinamide was effective in clearing the skin lesions (6). Another study of five participants treated with oral tetracycline and a mid-potency topical steroid showed a good response with no toxicity (7). A fourth open study of eleven participants used tetracycline (or doxycycline) and nicotinamide. Six participants had a complete response with a further two having a partial response (8).

Doxycycline is the tetracycline to be used in this study. It has fewer gastrointestinal side effects than oxytetracycline, has a better bioavailability and is easier to swallow as the tablets are smaller which should improve adherence. Indeed, in one study (8) doxycycline was used as an alternative therapy for participants unable to tolerate the gastrointestinal side effects of oxytetracycline.

The RCT described here will determine the effectiveness and safety of doxycycline (200 mg/day), which is widely available and inexpensive, versus prednisolone (0.5mg/kg bodyweight/day).

A search of the Controlled Trials Register indicates there are no current studies investigating tetracyclines as a treatment for bullous pemphigoid.

4.2. Details of Investigational Medicinal Products

4.2.1. Description

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

- Doxycycline (CAS number 564-25-0) available in either hyclate capsules or dispersible tablets.
- Prednisolone (CAS number 50-24-8) available in either tablets or dispersible tablets.

Participants will be prescribed study medication from the standard pharmacy supplies, so any brand may be prescribed. Detailed records of the form and brand of medication prescribed to the participant will be kept by pharmacy.

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

Participants will be also permitted to use betamethasone cream (CAS 378-44-9) as a rescue medication.

4.2.2. Packaging and Labelling

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

4.2.3. 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^{o}C.

The clinical trials pharmacist or designee at the hospital will dispense the medication and keep detailed dispensing records.

4.2.4. Known Side Effects

Doxycycline

Autonomic nervous system Flushing.

Body as a whole Hypersensitivity reactions, including anaphylactic shock, anaphylaxis, anaphylactoid reaction, anaphylactoid purpura, hypotension, pericarditis, angioneurotic oedema, exacerbation of systemic lupus erythematosus, dyspnoea, serum sickness, peripheral oedema, tachycardia and urticaria.

Central and Peripheral nervous system Headache. Bulging fontanelles in infants and benign intracranial hypertension in juveniles and adults have been reported in individuals receiving full therapeutic dosages of tetracyclines. In relation to benign intracranial hypertension, symptoms included blurring of vision, scotomata and diplopia. Permanent visual loss has been reported.

Gastro-intestinal Gastro-intestinal symptoms are usually mild and seldom necessitate discontinuation of treatment. Abdominal pain, anorexia, nausea, vomiting, diarrhoea, dyspepsia and rarely dysphagia. Oesophagitis and oesophageal ulceration have been reported in patients receiving Vibramycin. **Hearing/Vestibular** Tinnitus.

Haemopoietic Haemolytic anaemia, thrombocytopenia, neutropenia, porphyria, and eosinophilia have been reported with tetracyclines.

Liver/Biliary Transient increases in liver function tests, hepatitis, jaundice, hepatic failure and pancreatitis have been reported rarely.

Musculo-Skeletal Arthralgia and myalgia.

Skin Rashes including maculopapular and erythematous rashes, exfoliative dermatitis, erythema multiforme, Steven-Johnson syndrome and toxic epidermal necrolysis. Photosensitivity skin reactions and photo-onycholysis.

Superinfection As with all antibiotics, overgrowth of non-susceptible organisms may cause candidiasis, glossitis, staphylococcal enterocolitis, pseudomembranous colitis (with Clostridium difficile overgrowth) and inflammatory lesions (with candidal overgrowth) in the anogenital region. Similarly there have been reports for products in the tetracycline class of stomatitis and vaginitis.

Urinary system Increased blood urea.

Other When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discolouration of thyroid tissue. No abnormalities of thyroid function are known to occur. Tetracyclines may cause discoloration of teeth and enamel hypoplasia, but usually only after long-term use.

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 in patients receiving corticosteroid therapy.

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.

5. STUDY PURPOSE AND OBJECTIVES

5.1. Purpose

There is currently true clinical equipoise in the dermatology community between steroids and tetracyclines for the treatment of bullous pemphigoid. The purpose of this study is to determine whether doxycycline is sufficiently effective and safe to be used as a treatment for bullous pemphigoid.

The study consists of two comparisons, 1) a non-inferiority comparison of the effectiveness of doxycycline compared to prednisolone and 2) a superiority comparison of adverse events of the two treatments.

5.2. Hypothesis

The hypotheses for this study are that:

1) Doxycycline is not inferior in effectiveness to prednisolone in treating bullous pemphigoid given an accepted non-inferiority margin.

2) Doxycycline is less likely to result in severe adverse reactions than prednisolone.

5.3. Primary Objectives

- To assess whether doxycycline can be considered as non-inferior to prednisolone in effectiveness for the treatment of bullous pemphigoid given an accepted non-inferiority margin.
- To assess the safety of doxycycline compared with the prednisolone for the treatment of bullous pemphigoid.

5.4. Secondary Objectives

- To assess the cost-effectiveness of the two treatments.

6. STUDY DESIGN

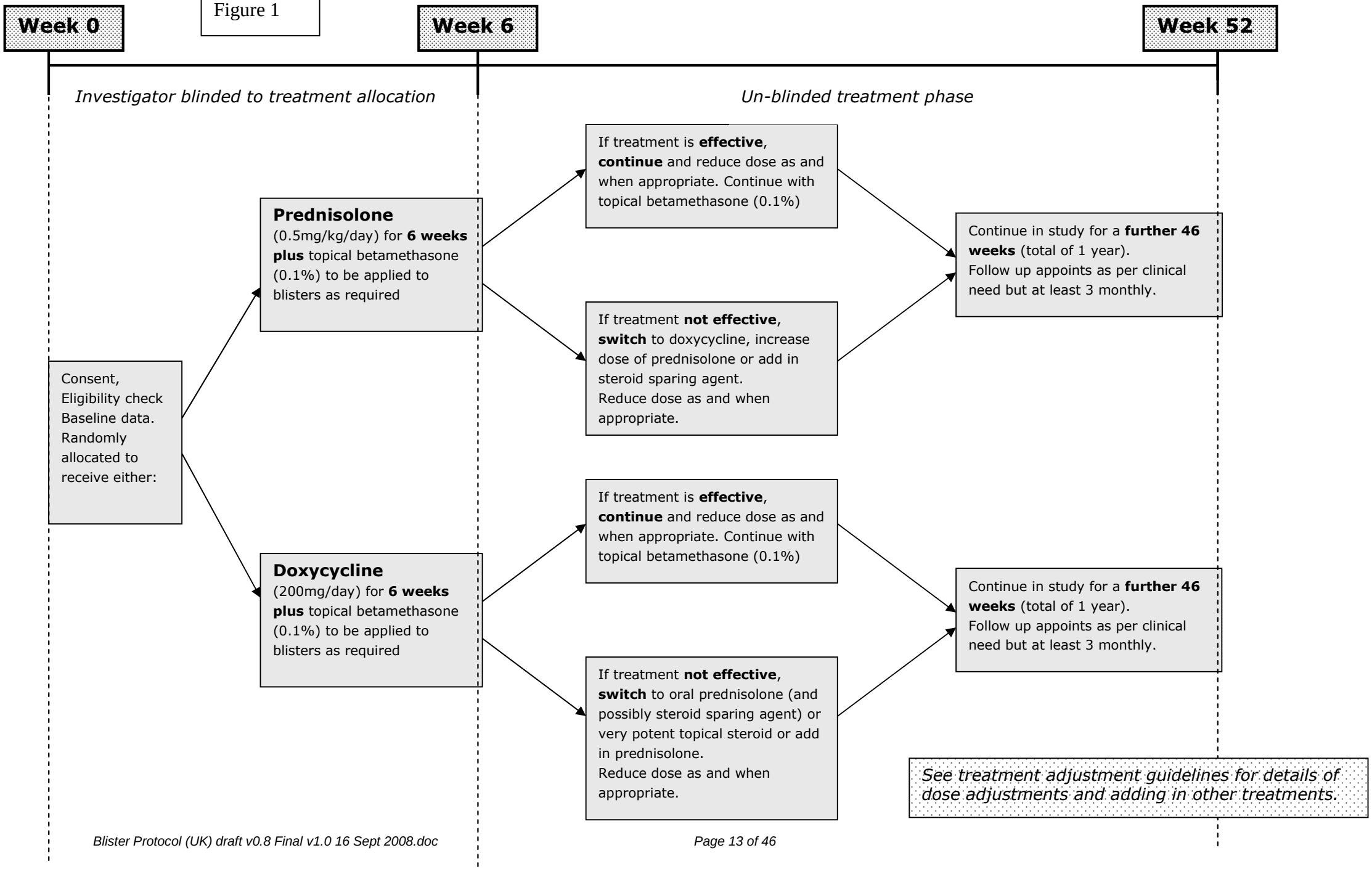
6.1. Overview

This study is a prospective, 2-arm, single-blind, parallel group, multi-centre randomised controlled trial. A total of two-hundred and fifty six participants will be recruited to the study (approximately two-hundred and ten in the UK). It is anticipated that there will be approximately 45 centres in the UK and 5 in Germany and the Netherlands.

At baseline (week 0), participants will be randomised to receive either prednisolone (0.5 mg//kg/day) or doxycycline (200mg/day) for 6 weeks. This is the set dose, single (investigator) blinded phase. From the 6 week visit onwards, the clinician will adjust the dosage to meet the clinical needs of the participant. All participants will be followed up for a total of one year from the date of randomisation, with visits a minimum of 3 monthly throughout the study.

An overview of the study design is shown in figure 1.

Figure 1



6.2. Outcome Measures

6.2.1. Primary Outcome Measures

- Difference between the two treatment arms in the proportion of participants classed as treatment success at 6 weeks. Treatment success is defined as 5 or less significant blisters present on examination at 6 weeks. Significant blisters are defined as intact blisters containing fluid which are at least 5mm in diameter. However, if the participant has popped a blister, or the blister is at a site that makes it susceptible to bursting such as the sole of the foot, it can be considered part of the blister count, providing there is a flexible (but not dry) roof present over a moist base. Mucosal blisters will be excluded from the count.

  A survey of the UK DCTN membership showed that a point estimate of 25% inferiority in effectiveness would be acceptable assuming a gain in the safety profile of at least 10%.

  This measure of success was selected as it was considered to be the more clinically relevant than a continuous measure of blister count. It would be less clinically relevant to perform an absolute blister count and report a percentage reduction. Instead, to state that treatment is considered a success if remission is achieved (i.e. the presence of five or less blisters on physical examination at 6 weeks) more closely reflects clinical practice. In addition, it is far less burdensome on investigators than including a full blister count, which would mean counting in the region of 50 – 60 blisters in many cases. This outcome measure will be performed as a single blind assessment.

- Difference between the two treatment arms in the number of reported grade 3, 4 and 5 (mortality) adverse events for one year following the start of study treatment. The Common Terminology Criteria for Adverse Events (CTCAE v3.0) will be used to grade adverse events. At each study visit, participants will be questioned about adverse events they have experienced since the last study visit (using a standard list of known side effects of the two study drugs).

6.2.2. Secondary Outcome Measures

- Difference in the proportion of participants in each treatment arm who are classed as treatment success (5 or less significant blisters present on examination at 6 weeks) **and** are alive at one year. This measure will provide a good overall comparison of the two treatment arms.
- Difference in the proportion of participants in each treatment arm who are classed as treatment success (5 or less significant blisters present on examination at 6 weeks) after 3 and 12 months of treatment.
- Difference in the proportion of participants in each treatment arm who have a further episode of bullous pemphigoid during their participation in the study after previously being classed as a treatment success. A relapse will be defined as “worsening of the disease that requires an escalation of therapy after the disease has been controlled”. This will compare relapse rates between the two treatments.

- Difference between the two treatment arms in the number of reported grade 1and 2 adverse events for one year following the start of study treatment. The Common Terminology Criteria for Adverse Events (CTCAE v3.0) will be used to grade adverse events. At each study visit, participants will be questioned about adverse events they have experienced since the last study visit (using a standard list of known side effects of the two study drugs). It is often the less medically important side effects that are of significant concern to patients taking corticosteroids, such as weight gain and skin fragility.
- Difference between the two treatment arms in the quality of life. Participants will complete the Euroqol EQ-5D and the Dermatology Life Quality Index (DLQI) questionnaires at baseline, 6, 13, 26, 39 and 52 weeks.
- Difference between the two treatment arms in cost-effectiveness. Data will be collected on health service usage (number, type and duration of visits to healthcare professionals, inpatient stays, drug costs) and will be used to calculate the average cost of the two regimens from an NHS perspective within the duration of the trial.

6.2.3. Tertiary Outcome Measures

- Difference in the proportion of participants in each treatment arm who, on examination at 6 weeks, are completely blister free (defined as completely free of all intact blisters and moist erosions). This outcome measure is included as some clinicians may prefer to see a complete clearance of the blisters as a measure of treatment success.
- Difference in the proportion of participants in each treatment arm who are alive 1 year after the start of study treatment.
- Difference in the proportion of participants in each treatment arm who, on examination at 3 weeks, are classed as treatment success (5 or less significant blisters present). This will compare the speed of onset of action between doxycycline and prednisolone.
- Difference in the amount of potent and super-potent topical corticosteroids used in each treatment arm during the study. A topical corticosteroid usage record card will be completed by the participant to record usage during the study.

6.3. Stopping Rules and Discontinuation

The following will result in the trial being terminated:

- Informal interim analysis and based on 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.

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.

6.4. Randomisation and Blinding

6.4.1. Randomisation

The randomisation will be based on a computer generated pseudo-random code using random permuted blocks of randomly varying size, created by the Nottingham Clinical Trials Unit (CTU) in accordance with their standard operating procedure (SOP) and held on a secure server. Access to the sequence will be confined to the Nottingham CTU Data Manager.

Participants will be allocated with equal probability to the doxycycline and prednisolone treatment arms. Randomisation will be stratified by disease severity. This is defined by the number of blisters present at baseline:

- Mild = 10 or less blisters
- Moderate = more than 10 but less than 30 blisters
- Severe = 30 or more blisters

Depending on local arrangements, to assign a treatment to the participant either the pharmacist or investigator will access the internet-based randomisation system, which will be developed and maintained by the Nottingham CTU. It is anticipated that in most study sites, the pharmacist will access the randomisation website, but in sites where this is not possible, the investigator will carry this out and a master list will then be used by the pharmacist to allocate treatment to ensure the investigator remains blinded to treatment allocation. Access to the randomisation website can either be directly via the internet or by telephone via the Nottingham CTU if web access is not available.

The sequence of treatment allocations will be concealed until interventions have all been assigned and recruitment, data collection, and all other trial-related assessments are complete. The statistical analysis will be performed using treatment code.

6.4.2. Blinding

The investigator will be blinded to treatment allocation for the initial treatment phase (week 0-6) during which the treatment regimen is fixed. At the week six visit, the investigator will carry out a physical examination and determine whether there are more than 5 significant blisters present for the primary efficacy outcome measurement. The investigator will remain blinded to treatment until the results of the primary efficacy outcome measurement are recorded in the randomisation database. This database will have an audit trail to demonstrate the study blind has been maintained.

The remainder of the study (weeks 7-52) will be un-blinded to allow the investigator to adjust the dose of study medication (and type of medication if necessary), particularly with prednisolone which needs careful tapering of the dose for safety reasons

To help maintain the study blind at the 3 and 6 week visits, three strategies will be employed to remind the participant not to reveal which treatment they have been taking:

1. The Trial Manager will telephone the participants immediately prior to the 3 and 6 week visits.
2. Investigators will remind participants when they first meet at the week 3 and 6 visits.
3. The clinic reception desk will be asked to give a reminder sheet to the participant when they arrive for the appointment.

In addition, investigators will be encouraged to, if possible, involve an independent person to conduct the baseline and week 6 blister count for the primary efficacy outcome measure. However, this is dependent of availability of staff at the recruiting centres.

Investigators will record if they had been un-blinded to treatment allocation before the primary efficacy outcome measure was carried out at the week 6 visit.

6.4.3. Procedures for breaking randomisation code

In the event that an investigator requires that the treatment allocation is revealed during the initial 6 week blinded phase of the study, they will use a web-based system hosted by the Nottingham CTU which will maintain an audit trail of any code breaks. They will be instructed not to approach the local pharmacy for this information. The investigator will be asked to provide the date, name of person requesting the blind to be broken, a reason why and any other relevant information within 48 hours of breaking the blind. The Trial Manager will be informed immediately of any code break by an automatic alert email.

It will be necessary to break the study blind to reveal the treatment allocation to allow the drug dose to be adjusted appropriately for participants wishing to withdraw during the first 6 weeks, Otherwise breaking the blind should only be done in the event of a medical emergency in which treatment is dependent on knowledge of the actual drug received. It should be noted that the blinding is only maintained for the first 6 weeks of the participants involvement in the study.

6.5. Trial Management

6.5.1. Trial Co-ordination

The trial will be managed from a central co-ordinating centre at the University of Nottingham, UK. The day-to-day co-ordination of the trial will be the responsibility of the Trial Manager who will be situated at the Nottingham Clinical Trials Unit. Dr Gudula Kirtschig (co-investigator) who will be based in Germany will co-ordinate the activities of the German and Dutch centres and will be responsible for co-ordinating the regulatory and ethics applications in Germany and the Netherlands.

The University of Nottingham will Sponsor the UK arm of the study and sponsorship of the study in the other European countries will be arranged with a leading centre in each country.

6.5.2. Trial Oversight Committees

The trial will be overseen by a trial steering committee (TSC), which will include an independent chair and two other independent members, along with the Chief Investigator, the Lead Clinician and other members as appropriate. The Trial Management group (TMG) will comprise the Trial Manager, Project Manager, Statistician, Lead Clinician 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 and Ethics Committee (DMEC) will also be convened for this study. All members will be independent of the applicants and study team. This committee will meet approximately three times a year and will oversee all ethical and safety issues. We will aim to appoint one member from each participating country.

6.6. Duration of Study and Participant Involvement

6.6.1. Duration of Participant Involvement in the Study

All participants will be in the study for one year. However, the duration of treatment will differ between participants; treatment will be continued until remission is achieved. For some participants this will be less than a year but it is likely that many will remain on treatment for the duration of the study. All participants will be followed up for a year after entering the study.

6.6.2. Duration of the Study

It is anticipated that recruitment will commence on 1st January 2009 and will continue for approximately 3 years. All participants will be followed up for one year so the last participant visit will be approximately 31st December 2012. End of the Study

The end of the study is defined as the last participant last visit (52 weeks).

6.7. Selection, Recruitment and Withdrawal of Participants

6.7.1. Participants

Newly presenting adults with bullous pemphigoid who have been blister free and received no treatment for bullous pemphigoid in the past year will be enrolled into this study. Children are excluded since this is almost exclusively a disease of the elderly. In addition, doxycycline is contraindicated in children under the age of 12 years old.

6.7.2. Setting

Participants will be recruited from approximately thirty hospitals in the UK and five hospitals in Germany and the Netherlands. Each centre will need to recruit approximately 7 participants over a 3 year recruitment period to meet the recruitment target. Recruitment may be extended to other European countries if recruitment rates are slower than anticipated. In the UK, study centres will be UK Dermatology Clinical Trials Network (UK DCTN) dermatologists in a mixture of district general and teaching hospitals. A survey of

the membership of the UK DCTN showed that, each dermatology department sees on average 14 new cases per year. Regular updates at department meetings and research / journal clubs will ensure all members of a department consider their bullous pemphigoid patients for the study.

6.7.3. Recruitment

The initial approach will be from a member of the patient's usual care team (which may include the investigator). 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 of all aspects pertaining to participation in the study.

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, but the consent forms and information sheets will not be available printed in other languages. It will be explained to the potential participant that 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 their data collected so far cannot be erased and will be used in the final analyses where appropriate.

In the UK, the majority of patients with bullous pemphigoid are referred to secondary care to be treated by a dermatologist. However, in some cases a general practitioner will initiate topical or systemic steroid treatment if bullous pemphigoid is strongly suspected before referring to secondary care. Since prior systemic treatment excludes patients from the study, a key aspect of the recruitment strategy will be to contact general practitioners in the local area so they are aware of the study and ask that they refer patients prior to initiating systemic therapy. The infrastructure of the UK DCTN will also be utilised to maximise recruitment rates in the UK. The Network has regional co-ordinators whose remit is to publicise studies in their region, sometimes covering several hospitals. These regional co-ordinators will be supported by the trial manager.

6.7.4. Inclusion criteria

- Aged at least eighteen years old.
- Able to provide written informed consent.
- Diagnosed with bullous pemphigoid defined as:
    - Clinical features consistent with bullous pemphigoid.
- To be eligible for the study, the patient will need to have **either** a positive direct **or** indirect immuno- fluorescence.
    - Direct **or** indirect (serum) immuno-fluorescence (linear IgG/C3 at epidermal basement membrane zone) positive for bullous pemphigoid.
- At least three significant blisters at two or more body sites that have appeared in the week prior to study enrolment. Significant blisters are defined as intact blisters containing fluid which are at least 5mm in diameter. However, if the participant has popped a blister, or the blister is at a site that makes it susceptible to bursting such as the sole of the foot, it can be considered part of the blister count, providing there is a flexible (but not dry) roof present over a moist base.

- Free of blisters and any treatment for bullous pemphigoid for at least one year.

Indirect (serum) immuno-fluorescence will be performed at a central laboratory (Oxford, UK) to maintain consistency across centres and to provide a more accurate diagnosis. The split skin technique which will be used is considered to be the most accurate diagnostic measure, but is not available at all centres.

If the results of the direct and indirect immuno-fluorescence are **both** negative for bullous pemphigoid then the participant will be withdrawn from the study. In normal practice, if there is a clinical picture of bullous pemphigoid, treatment is commenced and then changed later if the laboratory tests are subsequently negative. Therefore, the study will follow normal clinical practice as far as possible and it is anticipated that the number of incorrectly diagnosed participants will be low.

6.7.5. Exclusion criteria

The following criteria will exclude the patient from the study:

- Received any of the study medications or other recognised systemic medications for the treatment of this episode of bullous pemphigoid prior to study entry. Prior topical treatment is permitted.
- Recent administration of a live virus vaccine.
- Mainly or entirely mucosal bullous pemphigoid.
- Known allergy to tetracyclines.
- Presence of any condition which precludes the use of either of the study drugs.
- Women who are taking the oral contraceptive pill, who are pregnant or plan to become pregnant during the study duration or lactating. Women of childbearing potential must be using adequate contraception and be prepared to avoid pregnancy while participating in the study.
- Cancer (apart from basal cell carcinoma).
- Has any other condition which would, in the Investigators opinion, deem the patient unsuitable for participation in the study.
- Taking part in any other intervention study.

6.7.6. Retention of participants

To help retain participants on the study, in addition to being able to speak to the investigator, participants will be able to telephone the trial manager if they wish to discus any aspect of the study. For medical queries, the participant will be directed to a medical member of staff. In addition, the trial manager will make telephone calls to the participant to support them throughout the duration of the study. Participants will be sent birthday and Christmas cards whilst they are on the study, as well as regular newsletters updating participants of the progress of the study to help maintain participants in the study.

6.7.7. Withdrawal of participants from treatment and the study

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 may still be used in the final analysis. The reason for and date of withdrawal will be recorded on the case report form. All participants who withdraw from study treatment will be followed up for the remainder of the year providing they have not withdrawn consent.

Participants will be withdrawn from the study for the following reasons:

- Withdrawal of consent.
- Failure of participant to adhere to protocol requirements.
- A continuous break from the study medication of more than 3 days during the first 6 weeks and more than 3 weeks during the remainder of the study. If a break in study treatment is required, the reason must be recorded on the case report form.
- Participant unable to tolerate the study medication.
- For participants on the doxycycline arm, photosensitivity manifested by an exaggerated sunburn reaction. Treatment should be discontinued at the first evidence of skin erythema.

Note: the dose of prednisolone must be gradually reduced and should not stop abruptly.

Participants who have been randomised and then withdrawn because the laboratory tests show that they do not have bullous pemphigoid **will** be replaced. However, participants who withdraw after randomisation for any other reason will **not** be replaced.

6.7.8. Informed consent

All participants will provide written informed consent. Informed consent will be obtained from each participant before they undergo any study procedure.

Patients presenting with suspected bullous pemphigoid will be assessed by the recruiting investigator as per normal clinical practice. If this is strongly suggestive of a diagnosis of bullous pemphigoid, then the patient will be given details of the study (both verbally and a copy of the Participant Information Leaflet Summary). If the patient is interested in taking part, they will be given time to read the full Participant Information Leaflet and the investigator will answer any questions. Those wishing to participate will be required to sign a consent form before any study procedures are carried out.

Participants will be randomised to receive one of two standard treatments for bullous pemphigoid. For out-patients recruited to this study, if the disease severity is such that immediate oral treatment is required or the patient does not wish to delay the start of treatment, patients will be able to give their consent and be randomised to the study during their first visit to the dermatologist. Participants will be reminded that they are free to withdraw their consent at any time. Otherwise, the patient will be given a second appointment where they will give their consent and be randomised.

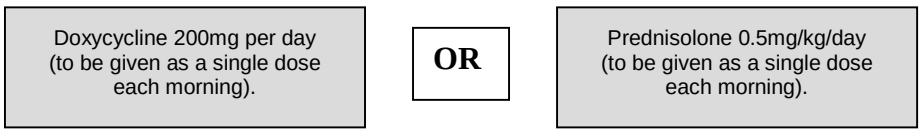
If the patient does not wish to take part or they are not eligible for the study, they will be treated in the normal way for their bullous pemphigoid.

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.

6.8. Study Treatment and Regimen

6.8.1. Study Treatment

At the baseline visit (week 0) participants will be randomised to receive, for weeks 0-6, either:



A study specific prescription form will be used for the participant to obtain their study drugs. For the dispensing at baseline, the prescription form will state that either prednisolone or doxycycline is to be dispensed according to the randomisation schedule, as the investigator is blinded to treatment allocation.

After 6 weeks, the prescription forms will state explicitly which study drugs are to be dispensed and the dose required.

Study medication will be dispensed at baseline and at each visit as required after week 6. The brand of study drug will not be specified and will be dispensed from normal pharmacy stocks. The investigator will be blinded to treatment allocation during this initial 6 weeks.

At the six week visit, the investigator will be un-blinded to treatment allocation (after the blister count has been carried out for the primary efficacy endpoint). The investigator is then able to adjust the study drug dose schedule according to clinical need. Investigators will be encouraged to adhere to the dose adjustment guidelines as far as possible and the reasons for any deviations from the guidelines will be recorded.

At any point, if the participant experiences a life threatening adverse reaction, they should be switched to the other study medication or another treatment, whichever is more appropriate in a clinical judgement.

6.8.2. Rescue Medication

For the weeks 0-3 and again after week 6, topical betamethasone valerate (0.1%) will be permitted. Topical betamethasone valerate (0.1%) will NOT be permitted during weeks 4-6 (i.e. the 3 weeks preceding the blister count for the primary effectiveness outcome measure). Participants will be instructed to apply topical betamethasone once a day to blisters / lesions as required (not to areas of unaffected skin). Topical betamethasone valerate (0.1%) will be dispensed as required.

If the participant is allergic to betamethasone, then an alternative topical steroid may be prescribed but this must be in the potent class. Otherwise, no other topical steroid is permitted during the study.

In addition, participants will be advised that they can apply a light moisturiser to blisters / lesions at any time during the study.

6.8.3. Prohibited Concomitant Medications

The administration of live virus vaccines is not permitted for all participants during weeks 0-6 as the investigator is blinded to treatment allocation, and must therefore warn all participants to refrain for having a live virus vaccine. However, after week 6, once the investigator knows which medication the participant is on, only those taking prednisolone will not be allowed live virus vaccines.

Participants should continue to take medications for other conditions as normal. However, if it is anticipated that the participant will need a live virus vaccine during the intervention phase, they will be ineligible for entry into the study.

6.8.4. Use of other antibiotics

If the participant requires antibiotics other than doxycycline or penicillin as an anti-infective treatment during the study, then they will remain in the study. They will be asked to continue with their doxycycline if possible.

6.8.5. Caution with other concomitant medications

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

- **Warfarin:** Tetracyclines depress plasma prothrombin activity and reduced doses of concomitant anticoagulants may be necessary. Participants should have appropriate monitoring of their prothrombin time as there have been reports of prolonged prothrombin time in patients taking warfarin and doxycycline.
- **Cyclosporin:** Doxycycline may increase the plasma concentration of cyclosporin. Renal tests will be done throughout the study as per normal; practice, but extra caution should be taken if cyclosporine is being co-administered.
- **Antacids:** The absorption of doxycycline may be impaired by concurrently administered antacids containing aluminium, calcium, magnesium or other drugs containing these cations; oral zinc, iron salts or bismuth preparations. Dosages should be maximally separated.
- **Penicillin:** Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving Vibramycin in conjunction with penicillin.
- **Methoxyflurane:** Caution is advised in administering tetracyclines with methoxyflurane due to rare renal toxicity.

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.

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

6.8.6. Adherence

To assess adherence, participants will be asked to record study medication usage in their diaries. The Trial Manager will also ask the participant about number of missed doses of study medication, using the diary as an aide memoir. Use of topical betamethasone will be recorded in a topical corticosteroid record sheet.

During the first six weeks of the study, more than three consecutive days of study medication missed will be a protocol violation. This is to ensure that the primary efficacy outcome is measured accurately. After the week six visit, more than three consecutive weeks of study medication missed will be a protocol violation.

6.8.7. Accountability

Detailed dispensing records will be kept by each dispensing pharmacy including participant study number and name, treatment given, batch number, expiry date, dose and date of dispensing. The study drugs will be appropriately labelled to meet with current clinical trials labelling regulations.

6.8.8. Management of study drug overdose

Overdose of study drug will treated as per normal clinical practice for overdose of doxycycline and prednisolone. If an overdose occurs in the first 6 weeks, then, if necessary, the investigator will need to be un-blinded to allow management of the overdose.

6.9. Study Visit Schedule and Procedures

6.9.1. Visit Schedule

As part of the development of this study, a survey of the UK Dermatology Clinical Trial Network members was undertaken to ensure the visit schedule reflects clinical practice as far as possible.

The visit schedule ensures that the relevant data are collected at appropriate time points balanced with the need for clinicians to be able to manage these bullous pemphigoid patients effectively. In addition, this is a multicentre study so the protocol needs to allow for differences in clinical practice between countries.

After the baseline visit at week 0, the primary effectiveness outcome measure at 6 weeks dictates the need for a mandatory study visit at week 6. A further mandatory study visit at 3 weeks is included to i) ensure the participant stops using topical betamethasone for the

next 3 weeks; ii) to assess any differences in the speed of onset of action between the two treatments.

After the week 6 visit, there are mandatory study visits at 13, 26, 39 and 52 weeks (+/- 3 weeks) to ensure participants are seen a regular intervals throughout the study. However, it is likely that, particularly early on in the treatment, participants will be seen more often than this. The frequency of extra visits will be dictated by clinical need on an individual participant basis. At these additional visits, only minimal data will be recorded.

In addition to clinic visits, participants will be telephoned by the trial manager or research nurse to provide extra support. This will include reminding participants not to reveal the treatment allocation to the investigator within the first six weeks of the study, checking adherence with study medication, reminders for appointments, clarifying data such as health service usage, explaining the study diaries and reminders to use them and answering any general queries the participant may have. In addition, the trial manger or research nurse may post some of the documents for the participants to complete at home, such as the Quality of Life questionnaires and the study diaries.

The telephone calls will be made as follows:

- Immediately post randomisation (introduction and answer any extra questions about the study that may have arisen since visiting the dermatologist).
- Immediately prior to the 3 week visit.
- Immediately prior to the 6 week visit.
- Every 6 weeks whilst the participant remains on study medication (post 6 weeks).
- Every 12 weeks once participant is no longer taking study medication.
- Any additional telephone calls as required to support the participant throughout the study.

Because this study is multicentre and multinational, there needs to be an element of flexibility in how the baseline visit is performed. In the UK, the majority of bullous pemphigoid patients are managed as outpatients. This means that when patients first present to dermatology during a standard clinic, there will be limited time available to carry out study procedures. Investigators may carry out standard clinical procedures to determine the diagnosis and discuss the study with the patient then schedule a return visit to obtain informed consent and carry out the baseline procedures including randomisation. However, bullous pemphigoid can sometimes present with a severity that required immediate treatment. If this is the case, or for other reasons it is necessary to begin treatment immediately, the patient may be given the information and given time to consider the study and randomised on the same day. Therefore, for the purposes of this protocol, the baseline visit is described as one visit but in reality this may be two clinic visits.

Procedures and Data Collection – blinded phase	Week 0 (baseline)	Week 3	Week 6
Clinical diagnosis of bullous pemphigoid	X		
Obtain informed consent	X		
Blister count and physical examination	X	X	X
Take samples for diagnostic tests: biopsy for direct immuno-fluorescence and blood sample for indirect immuno-fluorescence	X		
Ascertain the patient is eligible for the study.	X		
Collect medical history, other medication and demographic data	X		
Samples taken for routine blood tests[1]	X		
Give dietary advice for osteoporosis prevention	X		X
Determine Karnofsky score	X		
Complete quality of Life questionnaires (EQ-5D, DLQI)	X		X
Give study diary to participant	X	X	X
Collect adverse event, adherence, topical betamethasone (0.1%) usage and health service usage data		X	X

Procedures and Data Collection – un-blinded phase	Week 13	Week 26	Week 39	Week 52	Any additional visits
Blister count and physical examination	X	X	X	X	X
Samples taken for routine blood tests[1]		X		X	
Record any changes in bullous pemphigoid treatment (type and dose)	X	X	X	X	X
Record adverse events and changes in other medication	X	X	X	X	X[2]
Record study medication adherence and topical treatment usage	X	X	X	X	
Osteoporosis prevention measures (as required)	X	X	X	X	
Collect health service usage data	X	X	X	X	
Complete quality of Life questionnaires (EQ-5D, DLQI)	X	X	X	X	
Give study diary to participant	X	X	X		

[1] Blood tests will include (but will not be restricted to) full blood count, liver function tests, creatinine and urea. Blood tests will be done at least every 6 months, more often if clinically indicated.

[2] Only SAEs and SUSARs will be recorded at these visits.

Dispensing Medication - blinded phase	Week 0 (baseline)	Week 3	Week 6
Complete clinical trial prescription form	X		
Local pharmacist to dispense either prednisolone or doxycycline plus topical betamethasone (0.1%) according to randomisation schedule	X		
Start study medication; prednisolone or doxycycline plus topical betamethasone (0.1%)	X		
Stop topical betamethasone (0.1%)		X	
Complete prescription for appropriate medication for the bullous pemphigoid (un-blinded)			X
Restart topical betamethasone (0.1%)			X

From the 6-week visit onwards, the investigator is un-blinded to treatment allocation. Therefore, a prescription for the appropriate medication will be written as and when is necessary (i.e. when a resupply is needed or a change of medication or dosage is required). If the participant is continuing on prednisolone, from week 6, osteoporosis prophylaxis will be given in accordance with the BAD guidelines for treatment of bullous pemphigoid. These refer to the Royal College of Physicians guidelines for the management of gluco-corticoid induced osteoporosis and include consideration of bisphosphonates and lifestyle advice.

6.9.2. Week 0: Baseline visit

The initial visit will cover screening for eligibility and baseline assessments. In routine clinical practice, a dermatologist would commence treatment when the patient first presents to the dermatology clinic if bullous pemphigoid is strongly suspected, rather than waiting for the results of the diagnostic laboratory tests. Therefore, the study schedule reflects normal practice and allows randomisation to take place and treatment to commence at this first visit where appropriate. However, the protocol allows the baseline visit to be spread over two clinic visits if required and informed consent and randomisation to take place at the second visit. There could be a number of practical and ethical reasons for splitting the baseline visit into two including; i) the patient wishes to have more time to consider the study, ii) the dermatologist does not have enough time to undertake the study assessments during the first visit, iii) the disease severity is such that it is acceptable to delay starting treatment. For clarity, the baseline visit will be described here as one clinic visit.

The following procedures will be carried out at the baseline visit:

- Physical examination and confirmation of clinical diagnosis of bullous pemphigoid.
- Give the participant information leaflet to the patient. Discuss the study and answer any initial questions the patient may have. Allow patient sufficient time to consider their participation in the study. Discuss the study with the patient further and answer any questions about the study. Obtain consent from the patient before

proceeding with the study. NOTE: consent MUST be obtained prior to any study specific assessments or procedures being carried out.

- Conduct the blister count and establish disease severity defined by the number of significant blisters present:
    - Mild = less than 10
    - Moderate = between 10 and 30
    - Severe = more than 30
- Take samples for confirmation of bullous pemphigoid:
    - Biopsy for **direct immuno-fluorescence** and send to the local laboratory for analysis.
    - Blood sample for **indirect (serum) immuno-fluorescence** on salt-split skin (basement membrane zone) and send to central laboratory in Oxford, UK for analysis.
    - If a sample is sent for **histology** as part of routine clinical practice, the results of this will be recorded but this will not be a diagnostic entry criterion.

  It should be noted that these diagnostic tests would be done routinely as part of normal care for patients with suspected bullous pemphigoid. Therefore, they are not done for research purposes or . Therefore, if these have been ordered by another clinician then they will not be repeated for the purposes of the study. For the same reasons, there may be incidences where these are carried out before consent is obtained, providing they would have been part of the normal care for that individual patient, regardless of the study.
- Take samples for full blood count, kidney and liver function tests, plus any others that are clinically indicated. Collect sample for urine screen (sediment, protein and glucose). The results of these tests will not be collected or analysed but they should be checked by the clinician as per routine practice and any clinically significant findings treated accordingly and recorded on the medical history if appropriate.
- Check patient meets all eligibility criteria.
- Record relevant medical history and demographic data.
- Establish Karnofsky score (measure of activities of daily living (9).
- Ask the participant to complete quality of life questionnaires EuroQol EQ-5D and Dermatology Life Quality Index (DLQI).
- Give study diary to participant to record any medical problems, health service usage and adherence with study medication. Instruct the participant to return tube(s) at week 3 visit.
- Give general advice regarding osteoporosis prevention e.g. physical exercise, calcium in diet. This applies to all participants because at this point the investigator is blinded to treatment allocation.
- Randomise participant by logging on the web-based randomisation system or by telephoning the trial manager. The participant will be randomised to receive either

prednisolone (0.5mg/kg/day) or doxycycline (200mg/day) plus betamethasone valerate (0.1%) (either 3 x 30gm tubes or one100g tube) to be applied only to blisters for weeks 0-3 as required. Ask the participant to record topical betamethasone usage in the topical steroid usage card.

- Instruct the participant to take the completed the study prescription form to the local pharmacy (or appropriate alternative depending on local procedures) where study medication plus betamethasone will be dispensed.

If the baseline visit is spread over two visits to the clinic, consent will be obtained at the second visit. At the first visit, the participant information leaflet will be given to the patient and the investigator will explain the study. The patient will be given ONLY topical betamethasone cream (0.1%) and instructed to apply this to the blisters until the next visit. If the patient is allergic to betamethasone, then an alternative topical steroid in the potent class may be prescribed. If the investigator wishes to carry out the diagnostic tests at this visit before consent is obtained then this is acceptable provided they are not outside normal practice i.e. that they are NOT study specific procedures. The investigator will schedule a second visit for as soon as possible after this to obtain consent and to carry out the remaining screening and baseline procedures.

6.9.3. Week 3 visit

The purpose of the week 3 visit is to check the participants' progress, to record adverse events and to ensure the participant stops using topical betamethasone. There is a +/- 3 day window for this visit.

The following procedures will be carried out at the week 3 visit:

- Physical examination including counting the number of significant blisters present to determine extent of disease activity.
- Collect the used tube(s) of betamethasone. Explain to participant that they should use **NO** topical corticosteroids until after the week 6 visit when the primary efficacy outcome measure is recorded.
- Collect topical steroid usage card.
- Collect the completed study diary and record adverse event and health service usage data. Provide the participant with a new study diary to record any medical problems, health service usage and adherence with study medication.

6.9.4. Week 6 visit

At this visit, the number of significant blisters present will be recorded to determine whether the treatment has been a success (primary efficacy outcome measure). Following this, the investigator will be un-blinded to treatment allocation to allow adjustment of the study drugs for the remainder of the study. Guidelines for study drug adjustments are provided (see Appendix) and investigators will be encouraged to adhere to these wherever possible. There is a +/- 3 day window for this visit.

The following procedures will be carried out at the week 6 visit:

- Physical examination including counting the number of significant blisters present for the primary efficacy outcome measure.

- Contact the co-ordinating centre to obtain details of treatment allocation. Although the participant is not blinded to treatment allocation, this procedure should be followed to ensure that the blister count for the primary efficacy outcome measure has been recorded prior to the treatment allocation being revealed.
- For participants taking prednisolone, follow the Royal College of Physicians guidelines for the management of gluco-corticoid induced osteoporosis (consideration of bisphosphonates, bone mineral density scan and lifestyle advice).
- Complete quality of life questionnaires (EuroQol EQ-5D and DLQI).
- Collect the completed study diary and record adverse event and health service usage data. Report any relevant SAEs / SUSARs to the co-ordinating centre. Provide the participant with a new study diary to record any medical problems, health service usage and adherence with study medication.
- Record any dose / treatment adjustment and dispense study medication. Once the blister count for the primary efficacy assessment has been conducted and the investigator is un-blinded to treatment allocation, the study medication can be adjusted by the investigator as required.

6.9.5. Follow up visits at weeks 13, 26, 39 and 52 (open-label phase)

The remaining mandatory study visits are at weeks 13, 26, 39 and 52. However, it is likely that the participant will be seen more frequently, particularly early on in their treatment. There is a +/- 3 week window for these visits.

At these mandatory visits, the following procedures will be carried out at each visit:

- Physical examination including counting the number of significant blisters present to determine extent of disease activity / relapse of bullous pemphigoid.
- Complete quality of life questionnaires (EuroQol EQ-5D and DLQI).
- At weeks 26 and 52 **only**, take samples for full blood count, liver function tests, creatinine and urea, plus any others that are clinically indicated. Collect sample for urine screen (sediment, protein and glucose). The results of these tests will not be collected or analysed but they should be checked by the clinician as per routine practice and any clinically significant findings treated accordingly and recorded as an adverse event if appropriate.
- Collect the completed study diary and record adverse event and health service usage data. Report any relevant SAEs / SUSARs to the co-ordinating centre. Provide the participant with a new study diary to record any medical problems, health service usage and adherence with study medication.
- Record any dose / treatment adjustment and dispense study medication.

6.9.6. Extra visits

If the participant needs to be seen by the dermatologist for any visit extra to the mandatory visits at weeks 3, 6, 13, 26, 39 and 52, the investigator will be asked to capture a minimal data set at each extra visit.

The following procedures will be carried out at each extra visit:

- Physical examination including counting the number of significant blisters present to determine extent of disease activity / relapse of bullous pemphigoid.
- Report any relevant SAEs / SUSARs to the co-ordinating centre.
- Record any dose / treatment adjustment and dispense study medication.

6.9.7. Rupturing Blisters

Participants should be advised that they can rupture blisters if they are 5cm or over in diameter and are too uncomfortable to leave. They should be asked to not burst any blisters in the 3 days prior to a study visit.

6.9.8. Treatment of Relapses

Participants will be advised to return to the investigator for treatment if they have another episode of bullous pemphigoid. The visit schedule will remain with any extra visits occurring a described above. If the episode is treated by another clinician, then this will be picked up at the next regular study visit and recorded. In addition, GP records will be checked for relapses and participants will be asked to record any relapse in their study diary.

7. STATISTICS

7.1. Methods

The Trial Steering Committee will approve the statistical analysis plan and will also approve any amendments. Any deviations from the original plan will be documented and justified in the final report.

The analysis plan and statistical analysis will be carried out by the trial statistician under the supervision of Prof. Andrew Nunn, MRC Clinical Trial Unit. The trial statistician will analyse the results based on treatment code using a statistical analysis plan finalised prior to revealing the coded allocation sequence. Only after the analysis is complete will the actual treatment arms corresponding to the treatment codes be revealed.

In the comparison of effectiveness non-inferiority will be assessed using the lower bound of the 95% confidence interval for the difference between the proportion of participants who are classified as having a favourable outcome on the control, prednisolone arm and the doxycycline intervention. The analysis will be conducted by intention to treat (ITT) and per protocol. The intervention arm will be considered non-inferior in terms of effectiveness if the lower bound of the 95% confidence interval for the difference between the control and intervention arm in the ITT analysis is less than 37% and the results of the per protocol analysis are consistent with the ITT analysis.

In the comparison of adverse events the proportion classified as having had a grade 3 or higher adverse event will be compared using a chi-squared test of proportions after having stratified by centre; 95% confidence intervals for differences will be presented together with odds ratios and their 95% confidence intervals for differences in proportions.

Analyses adjusting for age and Karnofsky score (9) will also be performed.

7.2. Sample size and justification

A total of 256 participants will be recruited to the study (128 per arm). This should be sufficient to detect a clinically relevant difference of 20% in grade 3, 4 and 5 (mortality) side effects within one year of randomisation (primary safety objective). This is based on 60% incidence with prednisolone versus 40% with doxycycline at 80% power and 95% significance level allowing for a 20% loss to follow-up by one year. This estimation of side effect rate is based on a previous study looking at prednisolone for treatment of bullous pemphigoid (10). The authors showed that 60% of participants on 0.5 mg/kg/day reported grade 3 or 4 side effects after one year of treatment. We have used this figure for our study as this is directly comparable. The comparator arm in this published study was oral prednisolone. We have considered that this group is reasonably matched to our doxycycline group as they were not exposed to systemic corticosteroids and the associated side effects. The proportion of participants reporting grade 3 or 4 side effects in this group was 40%.

The outcome at 6 weeks will be expressed as a two sided 90% confidence interval for the difference in success rate (in terms of blister count) between the intervention, doxycycline arm and the control, prednisolone arm. It has been assumed that the point estimate for this difference will be 25%, based on an expected response rate of 95% in the control arm and 70% in the intervention. The lower level for the 90% confidence interval is the extent of inferiority that can be excluded based on the data from the trial. For the lower limit not to exceed a rate difference of 37% (corresponding to an absolute response of 58%) with 80% power, a total of 111 evaluable participants per group would be required. For it not to exceed 35% (an absolute response rate of 60%) 160 participants per arm would be required. If the point estimate for the difference is 20% for the lower limit not to exceed a difference of 32% (corresponding to an absolute response rate of 63%) with 80% power a total of 101 evaluable participants per group would be required, for it not to exceed 30% (an absolute rate of 65%), 146 participants per arm would be required. For the purpose of this study a lower level of response of 58% (95% - 37%) has been assumed; this is substantially greater than the complete lack of response that would be expected if participants remained untreated. A survey of the UK DCTN membership showed that a point estimate of 25% inferiority in effectiveness would be acceptable assuming a gain in the safety profile of at least 10%.

The primary effectiveness outcome measure is at 6 weeks. The attrition rate in the initial 6 weeks is likely to be low (5%). It should be noted that no spontaneous resolution of this condition would be expected at 6 weeks. However, due to the nature of the side effects of steroids, a higher drop out rate of 20% has been allowed for 1 year.

7.3. Primary analyses

- The difference between the two treatment arms in the proportion of participants classed as treatment success at 6 weeks will be analysed using a 95% confidence interval. An adjusted analysis will also be conducted including the stratification variable of disease severity, plus age and Karnofsky score.
- The difference between the two treatment arms in the number of reported grade 3, 4 and 5 (mortality) adverse events for one year following the start of study treatment will be analysed using a chi-squared test.

7.4. Secondary analyses

- The difference between the proportion of participants in each treatment arm who are classed as treatment success at 6 weeks **and** are alive at one year will be analysed using survival analysis, Kaplan Meier and Cox regression.
- The difference between the proportion of participants in each treatment arm who have a further episode of bullous pemphigoid during their participation in the study after previously being classed as a treatment success will be analysed using a chi-squared test.
- The difference between the proportion of participants in each treatment arm who, on examination at 3 months and 12 months are classed as treatment success will be analysed using a chi-squared test.
- The difference between the two treatment arms in the number of reported grade 1 and 2 adverse events for one year following the start of study treatment will be analysed using a chi-squared test.
- The generic Euroqol EQ-5D and the disease-specific Dermatology Life Quality Index (DLQI) questionnaires will be carried out at baseline, 6, 13, 26, 39 and 52 weeks to:
    - describe the temporal pattern of treatments on quality-of-life
    - correlate outcome measures and their sensitivity to variation and change
    - inform calculations of quality-adjusted life-years for each treatment.

  The difference in mean scores between the two treatment will be analysed.

7.5. Tertiary Analysis

- The difference between the proportion of participants in each treatment arm who, on examination at 6 weeks, are completely blister free will be analysed using a 95% confidence interval.
- The difference between the mortality rates in each treatment arm will be analysed using survival analysis, Kaplan Meier and Cox regression.
- The difference between the proportion of participants in each treatment arm who, on examination at 3 weeks are classed as treatment success will be analysed using a chi-squared test.
- The difference between the amount of potent and super-potent topical corticosteroids used in each treatment arm during the study will be analysed using a chi-squared test.

7.6. Cost Effectiveness Analysis

- Cost-effectiveness: profiles of resource use will be described and costed using national tarriff data where possible. Cost/QALY calculations and cost-consequence profiles will be used to compare treatments.
- The difference between the two treatment arms in cost-effectiveness: Data will be collected on health service usage (number, type and duration of visits to healthcare

professionals, inpatient stays, drug costs) and will be used to calculate the average cost of the two regimens from an NHS perspective within the duration of the trial.

- Health economic data will describe the cost-effectiveness of treatment selection from policy, clinical and patient perspectives. Resource use (number, type and duration of visits to healthcare professionals, inpatient stays, drug costs) will be used to calculate the average cost of the two regimens from an NHS perspective within the duration of the trial. These data will help establish whether any reduction in side-effects of doxycycline relative to prednisolone are associated with a subsequent reduction in costs to the NHS. A within trial cost-consequence profile will describe key physical consequences of the alternative treatments. Quality-adjusted survival data will be used to describe the temporal impact of the two treatments upon health-related wellbeing, to help inform patients and clinicians. Trial findings will be extrapolated over the remaining expected life of patients using epidemiological data and cost per quality-adjusted life-year gained (cost/QALY) estimates will be derived to inform policy decisions. The cost/QALY model will be parameterised using trial estimates and variances where possible. The influence of individual model parameters upon the robustness of findings will be explored using single parameter sensitivity analysis. Multiple parameter stochastic modelling will generate cost-effectiveness plane and acceptability curve data to explore the level of confidence in which either treatment is dominant and/or cost-effective.

8. ADVERSE EVENTS

8.1. Definitions

An **adverse event (AE)** is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.

An AE does include a / an:

1. Exacerbation of a pre-existing illness.
2. Increase in frequency or intensity of a pre-existing episodic event or condition.
3. Condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
4. Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

An AE does not include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead 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.

An AE does not include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead 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 occurring that results in any of the following outcomes:

- Death
- life-threatening
- Inpatient hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability / incapacity
- A congenital anomaly or birth defect in the offspring of a participant
- Other medical events may be considered to be a SAE if they require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All adverse events will be assessed for seriousness, expectedness and causality (not related, possibly related, probably related or definitely related). An adverse event whose causal relationship to the study drug is assessed by the Chief Investigator as "possible", "probable", or "definite" is an Adverse Reaction (AR). If the AR is classed as serious then it is a Serious Adverse Reaction (SAR).

All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause. The Chief Investigator shall be informed immediately of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners.

All adverse events will be assessed for seriousness, expectedness and causality:

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

8.2. Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as “unrelated” for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as “related” for notification purposes.

An AE whose causal relationship to the study IMP is assessed by the Chief Investigator as “possible”, “probable”, or “definite” is an Adverse Drug Reaction.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

8.3. Reporting of Adverse Events

Participants will be asked to contact the study site immediately in the event of any significant adverse event. All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause. The Chief Investigator shall be informed immediately of any reportable serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners.

In the event of a pregnancy occurring in a trial participant or the partner of 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. Where it is the partner of a trial participant consent will be obtained for this observation from both the partner and her medical practitioner.

All serious adverse events will be recorded and reported to the MHRA and REC as part of the regular mandatory reports. SUSARs will be reported within the statutory timeframes to the MHRA and REC as stated below. The Chief Investigator shall be responsible for all adverse event reporting.

8.4. Suspected Unexpected Serious Adverse Reaction (SUSARs)

A serious adverse reaction (SAR) that is unexpected (i.e. not a known side effect of the study drug) is classed as Suspected Unexpected Serious Adverse Reaction. All SUSARs will be reported immediately to the Chief Investigator and will require expedited reporting to the authorities as described below.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the study IMP.
- 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 MHRA.
- Shall inform the REC using the reporting form found on the NRES web page within seven days of knowledge of the event.
- Shall, within a further eight days send any follow-up information and reports to the MHRA and REC.
- Make any amendments as required to the study protocol and inform the ethics and regulatory authorities as required.

8.5. Participant Removal from the Study due to Adverse Events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

8.6. Collection of Adverse Event Data

This study is a comparison of two widely used drugs, prednisolone and doxycycline, for which the side-effect profile is well established. For this reason, only adverse events that are known side-effects will be collected (detailed in section 4.2.4, Known side effects).

At each mandatory study visit, the investigator will record whether the participant had experienced any of the reportable adverse events. The investigator will also have the opportunity to record any other significant adverse events that are not listed if deemed clinically relevant.

All available sources of information will be used to collect information on adverse events including hospital notes, the participant diary and discussion with the participant. Any adverse events reported will be graded according to the Common Terminology Criteria for Adverse Events v0.3.

9. Ethics Committee and Regulatory Aspects

9.1. Ethical and Regulatory Approval

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 Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics

Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires MHRA and 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 MHRA and REC. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, 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.

9.2. 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 designee will discuss the study with the patient and also give them a copy of the Participant Information Leaflet which will contain all the details of the study. There will be opportunity for the patient to ask questions about the study and the investigator or designee will ensure the questions are fully answered.

The investigator or their nominee and the participant shall both sign and date the Informed Consent Form before the person can participate in the study. The original will be kept in the Investigator Site File, one copy given to the participant and a copy will be retained in the participant's hospital records.

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.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

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).

9.3. Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation, for use on the case report forms (CRFs), other trial documents and the study 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 (dd/mm/yy).

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Participant Screening and Enrolment Log), to permit identification of all participants enrolled in the trial, in case additional follow-up is required.

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 black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

9.4. 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 questionnaires will serve as their own source data. Only trial staff as listed on the Site Responsibility (Delegation) Log shall have access to trial documentation other than the regulatory requirements listed below.

9.5. Direct access to source data / documents

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

Source documents provide evidence for the existence of the participant and permit verification of the data collected. Data reported on the CRFs that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

Source documents are filed at the investigator's site and may include (but are not limited to) participant diaries, current medical records, laboratory results, results of special investigations and pharmacy records.

9.6. Data Protection

Due respect for data protection and confidentiality will be maintained.

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. 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 (encrypted using a one way encryption method).

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 in encrypted format.

10. Quality Assurance and Audit

10.1. Insurance and Indemnity

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.

The University of Nottingham has taken out an insurance policy to provide indemnity in the event of a successful litigious claim for proven non-negligent harm.

10.2. Trial Conduct

This trial will be conducted in adherence 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 and SOPs 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. This training day will cover all relevant aspects of GCP and all study procedures and SOPs. In addition, the trial manager will visit sites where necessary to conduct further training and provide assistance. Further training on GCP will be accessed through the UKCRN training programme which all UK DCTN members can access free of charge.

10.3. Trial Monitoring and Audit

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.

Trial data at sites will be primarily monitored under existing governance arrangements. However, the trial manager 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 by the Trial Manager or designee at least yearly and an audit report shall be made available to the Trial Steering Committee.

10.4. Record Retention and Archiving

In compliance with the ICH/GCP guidelines, regulations and in accordance with University of Nottingham 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 at the University of Nottingham.

10.5. Risk Assessment

There is little additional risk or benefit to the individual participant by entering this study. Both study drugs are standard treatments for bullous pemphigoid 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.

10.6. Confidentiality

Individual participant medical information obtained as a result of this study is 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.

Such 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, representatives of the Sponsor, the ethics committees, host institutions and the regulatory authorities.

11. 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 European Blister Study Team. All Principle and co-investigators will be named in the acknowledgements, detailing their role in the study. Participants will not be identified in any publications.

12. USER AND PUBLIC INVOLVEMENT

In the UK, a patient panel of 5-7 people who have had, or still have, bullous pemphigoid will be involved in this study, plus a smaller panel of 2-3 patients from Germany and the Netherlands. Members of the panels have been identified through the UK Bullous Pemphigoid Support Group and clinicians on the study team. One panel member will be invited to contribute to steering committee meetings where appropriate.

The patient panels will contribute to the design of the study and the content of the participant information leaflets and other documents given to participants with the aim of increasing the acceptability and relevance of this research to patients.

13. STUDY FINANCES

13.1. Funding source

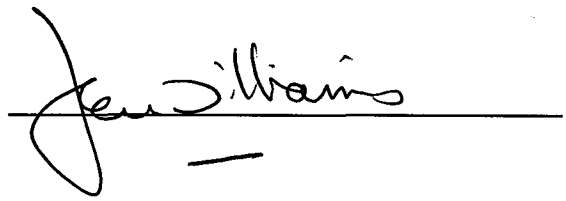
This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (Department of Health, UK).

13.2. Participant stipends and payments

Participants will not be paid to participate in the trial. Travel expenses will be offered for any costs incurred for hospital visits in excess of usual care, and will be in the form of vouchers wherever possible.

14. Signature Page

Chief Investigator: PROFESSOR HYWEL C. WILLIAMS

Signature:  **Date:** 16th September 2008

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:** _____

15. References

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(3) F Wojnarowska, G Kirtschig, AS Highet, VA Venning, NP Khumalo BAD guidelines: Guidelines for the Management of Bullous Pemphigoid Br J Dermatol, Vol. 147, 2002 (p.214-221)

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(6) Kolbach DN, Remme JJ, Bos WH, Jonkman MF, De Jong MC, Pas HH, van der Meer JB. Br J Dermatol. Bullous pemphigoid successfully controlled by tetracycline and nicotinamide. 1995 Jul;133(1):88-90.

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(8) Goon AT, Tan SH, Khoo LS, Tan T. Tetracycline and nicotinamide for the treatment of bullous pemphigoid: our experience in Singapore. Singapore Med J. 2000 Jul;41(7):327-30.

(9) Karnofsky DA, Burchenal JH. *The Clinical Evaluation of Chemotherapeutic Agents in Cancer*. In: MacLeod CM (Ed), "Evaluation of Chemotherapeutic Agents." Columbia Univ Press, 1949: 196.

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16. Appendix

16.1. Karnofsky Performance Status Scale Definitions Rating (%)

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

16.2. Blood and Urine Tests

As a minimum, the following blood tests will be carried out prior to taking any study drugs:

- Full blood count.
- Liver function tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin and gamma-glutamyl transferase (GGT).
- Kidney function tests (urea and creatinine).

However, this list is not designed to be exhaustive, further tests should be ordered as clinically necessary.

A urine sample will be tested for sediment, protein and glucose.

16.3. Dummy Example Allocation List

A master list prepared and held by Nottingham CTU. A dummy example of how this might look is shown below:

Participant number	Treatment	Participant number	Treatment
0001	Prednisolone	**0015**	Doxycycline
0002	Prednisolone	**0016**	Doxycycline
0003	Doxycycline	**0017**	Doxycycline
0004	Doxycycline	**0018**	Prednisolone
0005	Doxycycline	**0019**	Doxycycline
0006	Prednisolone	**0020**	Prednisolone
0007	Doxycycline	**0021**	Prednisolone
0008	Prednisolone	**0023**	Doxycycline
0009	Prednisolone	**0024**	Prednisolone
0010	Doxycycline	**0025**	Doxycycline
0011	Prednisolone	**0026**	Prednisolone
0012	Doxycycline	**0027**	Doxycycline
0013	Prednisolone	**0028**	Prednisolone
0014	Doxycycline	**0029**	Doxycycline

The pharmacist at each centre will keep a record of the treatment allocation as in the example below:

Participant Study number	Participant name	Treatment allocation	Batch number	Expiry date	Date of dispensing
0002	Paul Smith	Prednisolone	34/65	08/2009	21/09/2008
0015	Tim Bowen	Doxycycline	54/77	10/2010	14/01/2009
0026	Judy Jones	Prednisolone	54/77	10/2010	02/02/2009

There will be a record sheet for each participant to record all dispensing episodes as in the example below:

Participant Study number	0002	**Participant name**	Paul Smith		
	Date of dispensing	**Name of drug**	**Total mg dispensed**	**Batch number**	**Expiry date**
Visit 1 (Screening / baseline)	02/09/2008	Prednisolone	30mg	34/65	08/2009
Visit 2 (week 3)	23/09/2008	Prednisolone	30mg	34/65	08/2009
Visit 3 (week 6)	14/10/2008	Prednisolone	25mg	34/65	08/2009
Visit 4 (extra visit)	11/11/2008	Prednisolone	25mg	54/77	10/2010
Visit 5 extra visit)	09/12/2008	Prednisolone	20mg	54/77	10/2010