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

Health Economics Analysis Plan

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1 Introduction

1.1 Study Background

Bullous pemphigoid is the most common autoimmune blistering disease in Western Europe, occurring mainly in the elderly, with significant morbidity and mortality. In particular, widespread blistering, skin erosions and severe itching cause distress and pain. Bullous pemphigoid is frequently treated with oral corticosteroids which, it is thought, contribute to the high mortality and morbidity rate of treated patients. A Cochrane review has suggested that treatment with tetracyclines may be effective but that there is a lack of high quality, randomised controlled trials to confirm this. The BLISTER trial was designed to determine the effectiveness and safety of doxycycline compared with prednisolone for the treatment of bullous pemphigoid.

BLISTER is a multi-centre, randomised, controlled trial of 52 weeks duration with two parallel arms: 200mg/day of doxycycline for 6 weeks or 0.5mg/kg/day of prednisolone for 6 weeks; from weeks 6 - 52, investigators can amend the medication in line with patient need. A total of 256 patients with bullous pemphigoid from the United Kingdom and Germany are being recruited into the study.

The primary outcomes are i) effectiveness, measured by an assessor-blinded blister count at week 6 and ii) safety, measured by the proportion of patients experiencing adverse events during the year of follow up that are related to the trial medication and graded as 3 or above (using the Common Terminology Criteria for Adverse Events version 3.0). Secondary outcomes include relapse rates, the number of patients experiencing any grade of adverse event related to treatment, death, quality of life and cost effectiveness. The primary analysis for effectiveness will be to assess whether doxycycline can be considered non-inferior to prednisolone at 6 weeks; analyses will be conducted both by per protocol and intention to treat. The primary analysis for safety is a superiority analysis and will be by intention to treat. Planned recruitment was completed by September 2013 and results will be available from March 2015.

1.2 Health Economics Objective

The BLISTER trial objectives, inclusion criteria, sample size, endpoints and analysis plan are described within the study protocol.

This document describes the planned cost-effectiveness analysis, where the objective is to establish the relative cost-effectiveness of oral doxycycline-led and oral prednisolone-led therapy using incremental cost and cost-effectiveness analyses using disease specific and generic quality of life measures - Dermatology Life Quality Index (DLQI) and Euroqol (EQ-5D-3L and EQ-VAS).

1.3 Health economics Analysis Plan

The objective of this analysis plan is to describe the cost-effectiveness analyses to be carried out for the BLISTER randomised controlled trial for the final analyses. It does not address the trial analysis set out in Statistical Analysis Plan (SAP). Analyses will be conducted by model building in Excel, producing macro-generated bootstrapped estimates of cost-effectiveness to generate (within-trial) incremental cost-effectiveness ratio (ICER) planes and cost-effectiveness acceptability curves (CEAC) using standard methods.

2 Analysis

2.1 Study Perspective

All analyses will be at the patient level, by intention to treat and will take a NHS perspective.

2.2 Contributory Outcomes

2.2.1 Resources

Resource use is recorded by asking patients to recall: GP clinic and home visits, practice and district nurse visits, outpatient visits and inpatient stays. Resource assessments occur at 3, 6, 13, 26, 39 and 52 weeks. Collection of data occurs at mandatory clinical visits, augmented by telephone calls. Healthcare resource use will be costed using published national reference costs [1,2]. Costs of study medications will also be included using British National Formulary Tariffs [3]. Patient level costs will be estimated as the sum of resources used weighted by their National reference costs. Effect of treatment on resource use and cost will be estimated using Student's t-test for unpaired data and bootstrapping.

2.2.2 Quality of Life

The trial includes the use of the Dermatology Life Quality Index (DLQI) [4] and Euroqol (EQ-5D-3L and EQ-VAS) [5] questionnaires, which will be completed at baseline, 6, 13, 26, 39 and 52 weeks. Repeated scores over time will be used to construct area-under-curve (AUC) estimates for each patient, using the trapezoidal method. The within trial difference in quality-adjusted survival expressed as quality-adjusted life years (QALYs) gained will be estimated using the EQ-5D-3L measure with the EQ-VAS providing a supportive estimate. No discounting will be applied to quality-adjusted survival data reflecting the follow-up period (< 1 year). Effect of treatment on quality of life measures will be estimated using Student's t-test for unpaired data and bootst.

2.2.3 Cost-Effectiveness Analysis

Patient-level cost and quality of life data will be bootstrapped (sampled with replacement, N=10,000) to populate incremental cost effectiveness (ICER) planes, to estimate average (median) cost-effectiveness and pseudo 95% confidence interval (2.5 and 97.5 centile values) [6,7]. Findings will be visualised by generating cost-effectiveness acceptability curves (CEAC).

3 References

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