SINS ANALYSIS PLAN

This analysis plan was written after recruitment and during the last part of the 3-year follow-up phase.

1. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

1.1. Summary of study background & explanation of rationale

Basal cell carcinoma (BCC), or "rodent ulcer" is the commonest human cancer affecting at least 30,000 UK people annually. Although not life threatening, these cancers destroy the skin and neighbouring tissues, causing significant cosmetic disfigurement especially on the face. Basal cell carcinoma is increasing, probably due to increased ultraviolet exposure, yet it remains one of the most poorly researched forms of human cancer. Most of these cancers are treated surgically in hospital dermatology and surgery departments, yet current treatment provision is saturated.

Studies have suggested that a cream formulation of imiquimod, a drug that enhances the body's immune response, may be effective at treating BCC. Although not as good as surgery, it is possible that the cream will result in a better cosmetic result. This, with the added convenience of home application, may herald a major new way of treating many people with uncomplicated BCCs in the UK. We would therefore like to do an independent and definitive randomised controlled trial of imiquimod cream versus surgery, looking at disease recurrence at 3 years as the main outcome. We also wish to see whether some genes can identify which people are going to respond best to treatment.

Based on Phase II data, it is highly unlikely that imiquimod will be superior to excisional surgery. Therefore rather than seeking therapeutic equivalence within a pre-specified range, the study is essentially a non-inferiority study ie the imiquimod success rate will be no worse than a pre-determined lower acceptable level.

1.2. Objectives and aims

The study aims to determine the effectiveness of imiquimod 5% cream compared with excision surgery for the treatment of superficial and nodular basal cell carcinoma presenting in low risk areas.

The specific research questions to be answered are:

- Can imiquimod 5% cream applied topically give an acceptable and clinically useful success rate (3 year clinical clearance) and acceptable side effect profile when compared with excision surgery for superficial and nodular BCC at low risk sites?
- Is imiquimod more cost effective than surgery for low-risk BCC?
- Does imiquimod result in a more aesthetically acceptable result than conventional excision?
- Do certain phenotypic patient characteristics and gene polymorphisms predict tumour responsiveness to imiquimod treatment?

Details of the proposed analysis of the genetic component of this study are not included in this analysis plan since these will be dealt with separately.

1.3. Patient population studied

Men and women of any age with a histologically confirmed primary nodular or superficial BCC in a low risk area.

1.4. Trial configuration

Prospective, multi-centre parallel group, open labelled, randomised non-inferiority trial.

1.5. Randomisation procedures

All participants eligible for inclusion in the study and for whom consent had been obtained were to be randomised to topical imiquimod or surgery according to a pre-prepared randomisation schedule once suitable histological biopsy results were obtained. The randomisation schedule was generated by computer by staff at the Trent Research and Development Support Unit (TRDSU). The group to which participants were allocated was obtained while the participant was attending their baseline visit, using a central telephone randomisation service run by independent staff at the TRDSU. Patient details were entered irrevocably before the researcher was informed of the group to which the participant had been randomised.

Randomisation was stratified according to whether the lesion was nodular or superficial (defined clinically and confirmed by histology) and by centre. No attempt to equalise numbers of nodular and superficial BCCs randomised was made.

Deviation from protocol procedure (13/10/03)

In three centres (QMC, KMH, Lincoln) randomisation took place before histological results were available. Participants were withdrawn if later histology did not confirm the lesion to be a BCC.

1.6. Blinding

Due to the nature of the interventions it was not possible for participants and staff administering the treatments to be blinded (masked) to the interventions. The components of the study that were blinded are the assessment of the cosmetic appearance of the lesion site (achieved by an outcome assessor using photographs) and the analysis of the data. In the analysis of the data, treatment groups will be distinguished by a code and the meaning of the codes will not be revealed until the analysis is complete.

1.7. Safety, data monitoring or special steering or evaluation committees

An independent Data and Safety Monitoring Committee comprising of a dermatologist, epidemiologist and statistician was set up to meet once a year. The remit of this committee was to consider safety issues and to make decisions on the fate of the study in the light of interim analyses. The committee was also responsible for reviewing data relating to severe skin reactions with the trial statistician.

1.8. Interim analyses

It was agreed that prespecified safety reviews would take place when the first 6 month data are available and that the study would operate to one clear early stopping rule. The purpose of this *early stopping rule* was to safeguard participants with nodular BCC against unacceptably low early clearance rates from imiquimod. Thus, if after 100 participants with nodular BCC, the success rate was lower than 60% in the imiquimod group at the 6-month assessment then the data monitoring committee would consider recommending stopping the trial for participants with nodular BCC. In this context, "success" meant those who failed to show adequate clinical response to the cream plus those

who dropped out due to unacceptable local side effects. This percentage represents the lowermost 98% confidence interval (exact method) for a success rate of 70%. A 6-month assessment point was chosen in favour of a 3-month point, as participants with nodular BCC would still be receiving cream until 12 weeks and it was necessary to allow ample time for any treatment-induced inflammation/scaling to settle before assessing whether there was any remaining tumour clinically.

It was also agreed that if the study needed to be stopped for those participants with nodular tumours because of unacceptably low initial clearance rates, then the study would continue for superficial BCCs. No stopping rule was developed for superficial BCC tumours because of the much higher success rates for superficial BCC in Phase II studies.

No adjustment for the above planned interim analysis was to be made since the stopping rule relates to the imiquimod group only and no direct comparison between the two treatment groups is being made.

Deviation from protocol procedure

On 07/06/04 the trial co-ordinator sought advice from the Data Monitoring Committee (DMC) on whether the proposed interim analysis should be conducted since at that point the recruitment rate was much lower than anticipated (136 participants in total over a 12 month period) and only just over half of the lesions were nodular as opposed to the 85% that were expected. If recruitment rates were to continue at the same rate as the current rate it would be at least a year's time before 6 month data would be available for 100 patients with nodular tumours and approximately two thirds of the total number of patients for the trial would already have been recruited. After consideration of this issue by the DMC is was agreed that no changes to the stopping rule would be necessary since looking at the data earlier would probably be unhelpful as the sample would be too small to draw any conclusions. Therefore no interim analyses were performed.

1.9. Final Analysis Efficacy and Safety Variables

The primary efficacy measure is the comparison of the proportion of participants with clinical evidence of "success" at 3 years (defined as no evidence of treatment failure and no sign of recurrence at, or before 3 years as determined clinically) by treatment group.

The secondary efficacy measures are the comparison of the following by treatment group:

i) The proportion of successes (as defined above) at 1, 2 and 5 years.
ii) Time to first recurrence
iii) The proportion of participants rating the cosmetic appearance of the lesion site as good or excellent at 6 months (short term result) and at 3 years (long term result).
iv) The proportion of participants with lesion site rated by an independent blinded dermatologist as good or excellent at 6 months and at 3 years.
v) The proportion of participants experiencing a moderate or more severe level of pain: a) during the treatment period; b) during the 16 week follow up period after treatment.
vi) The median number of days participants experience a moderate or more severe level of pain: a) during the treatment period; b) during the 16 week follow up period after treatment.
vii) Cost effectiveness for the different treatment modalities to include number of participant visits to hospital, as well as cost of treatment per session.

The safety and tolerability variables that will be compared by treatment group are:

i) The proportion of participants who experienced an adverse event in first 6 months from the start of treatment.
ii) The proportion of participants who experienced a possibly treatment related adverse event in the first 6 months from the start of treatment.
iii) The proportion of participants who experienced an adverse event throughout the duration of the trial.
iv) The proportion of participants who experienced a possibly treatment related adverse event throughout the duration of the trial.
v) The proportion of participants who experienced a serious adverse event.
vi) The proportion of participants who experienced an adverse event of at least moderate severity.
vii) The proportion of participants who experienced an adverse event which led them to withdraw from the trial.
viii) The proportion of participants who experienced an adverse event for which medication was taken.
ix) The proportion of participants who experienced an adverse event for which a change of imiquimod dose was necessary.

The following safety and tolerability variables will also be reported for the imiquimod group:

i) The proportion of participants who did not receive sufficient exposure to imiquimod treatment as result of a treatment related adverse event.
ii) The proportion of participants who did not receive sufficient exposure to imiquimod treatment as result of a non-treatment related adverse event.
iii) The median number of days participants experienced itching of the randomised BCC during the treatment period (imiquimod group only).
iv) The median number of days participants experienced itching of the randomised BCC in the 16 weeks after treatment (imiquimod group only).
v) The median number of days participants experienced weeping of the randomised BCC during the treatment period (imiquimod group only).
vi) The median number of days participants experienced weeping of the randomised BCC in the 16 weeks after treatment (imiquimod group only).

Compliance in the imiquimod group will be measured by the total number of days the participants used the cream and in the surgery group, by the receipt of surgery.

Sufficient exposure is defined as: ≥4weeks treatment for superficial BCCs; ≥8 weeks treatment for nodular BCCs. The number and percentage of participants who had insufficient exposure to imiquimod cream will also be reported.

1.10. Determination of Sample Size

The original sample size calculations were based on a 97% success rate for surgery and a 90% success rate for imiquimod cream, with a lower 98% confidence boundary of 84%. This figure of 90% was considered to be the lowest percentage that fellow dermatologists would consider changing their

practice, if imiquimod was found to be easy to use and acceptable in terms of side effects. This was based on the belief that other commonly used treatment modalities such as curettage or cryotherapy had success rates approaching 90%[3].

Assuming a 1-tailed significance level of 1%, and 80% power, a total sample size of 740 participants was required to demonstrate non-inferiority when 3 year success rates of 97% in the surgery group and 90% in the imiquimod group, with a lower 98% confidence limit of 84% are assumed.

Due to recruitment difficulties the sample size was revisited (March 2006). It was considered how the lower 98% confidence interval would vary according to different success rates for imiquimod and surgery based on 400, 450, 500, 550 and 600 participants (still assuming 80% power and 1% one-sided statistical significance). Calculations indicated that the additional gain in power from 400 to 600 participants in terms of the precision of the low 98% confidence interval would be small assuming an overall success rate of 97% for surgery (likely due to following 4mm excision margins where possible). A sample size of 500 would allow the lower confidence interval to be within less than 10 percentage points of the actual imiquimod success rate assuming the imiquimod success rate is at least 70%. It was the view of the Trial Steering Committee (which met on 22nd March 2006 and included 3 clinicians) that such a precision is probably acceptable for influencing practice. The new NICE guidance on managing BCC in the community gives timeliness of results as important in guiding future imiquimod use. Even an overall success rate of around 70% could still be useful for dealing with simple BCC in the community, providing the long term follow up data is supportive. In summary, it was agreed to aim for a revised overall sample size of 500 which should be both useful and achievable.

1.11. Changes in the Conduct of the Study or Planned Analysis

Since randomisation took place before histological confirmation in 3 centres, some participants who were randomised were not eligible for inclusion in the study because the biopsy showed they did not have a BCC. These participants did not continue in the study so no outcome data are available. These participants will be excluded from the analysis. The number and percentage of ineligible participants will be reported by treatment group in the protocol deviations section (see section 2.3 for details).

2. GENERAL ANALYSIS CONSIDERATIONS

As the study is a pragmatic parallel group randomised, non-inferiority trial with a usual (control) treatment arm, data will be reported and presented according to the extended CONSORT Statement for reporting of Non-inferiority and Equivalence Randomized Trials (Piaggio et al 2006).

2.1. Types of analysis

2.1.1. Assessing efficacy

2.1.1.1. Primary outcome

The principal analysis will be the comparison of the proportion of participants successfully treated at 3 years (as determined clinically) by treatment group. The sample size is based on the confidence interval for the absolute difference in success rates between treatment groups but this will be translated into relative risks for the analysis. This is because the acceptability of a given absolute treatment difference may differ according to the success rate of the standard treatment (in this case, surgery) and

also because we felt that clinicians would be able to interpret relative risks more easily than odds ratios. The relative risk will be used to indicate the risk of being treated successfully in the imiquimod group relative to the risk of being treated successfully in the surgery group.

Poisson regression with a robust error variance will be used to estimate treatment effect, with centre and BCC type (fixed effects) included as covariates. This method of analysis was chosen instead of the usual choice of analysis for binary outcome measures, logistic regression, since as indicated above we wanted to present relative risks rather than odds ratios and the event of interest (successfully treated) is not a rare event. Poisson regression has been shown to be a reliable method to use for estimating adjusted relative risks for prospective studies with binary outcome variables (Zou(2004)). The robustness of these findings will be assessed by including baseline variables that are associated with the outcome (see section 4.2.2 for details) as covariates in the model. Akaike's information criterion (AIC statistic) will be used to compare the performance of different models. Overdispersion will be tested for using the likelihood ratio test on the parameter alpha and if there is evidence of overdispersion, negative binomial regression models will be fitted. Relative risks and 98% confidence intervals will be presented for the model with the lowest AIC.

The overall fit of the models will be assessed using the Pearson and the deviance "goodness of fit" statistics. Observed and predicted probabilities for each value of the outcome variable will be compared visually by plotting these on a graph and also by calculating the chi-square goodness of fit test. Normal probability plots and the Shapiro-Wilk test will be used to assess whether the Pearson residuals can be assumed to have come from a Normal distribution. Pearson residuals will also be plotted against predicted means.

2.1.1.2 Secondary outcomes

i) The secondary outcome variables, the proportion of participants successfully treated at 1, 2 and 5 years will be analysed using the same method as described above for the primary outcome variable.

ii) Time to first recurrence will be compared between treatment groups using ordinal regression analysis, adjusting for centre and BCC type (fixed effects). The continuation ratio method will be used since the time at which recurrences occur is recorded in ordered categories, namely the time interval between consecutive follow-up visits (see section 4.1 for further details). Participants will progress through the ordered categories until a recurrence has occurred, at which point they remain in that category.

Further models will be fitted where the effect of including the variables that were explored for inclusion in the model for the primary outcome (see section 4.2.2) as covariates in the model will be examined. Akaike's information criterion (AIC statistic) will be used to compare the performance of different models. Odds ratios and 98% confidence intervals will be presented for the model with the lowest AIC.

The goodness of fit of the final model will be assessed by the Pearson chi-square and deviance statistics. The assumption of proportionality will be assessed using the likelihood–ratio test obtained using the "test" option of the "ocratio" stata command. The accuracy of the

classification of results for the time to first recurrence categories will be displayed in a 5x5 classification table where actual and predicted response categories are cross-tabulated against each other.

iii) The proportion of participants with a lesion of excellent or good appearance as determined by the participant, and similarly as determined by the independent dermatologist, will be analysed using the same method as described above for the primary outcome variable (section 2.1.1.1).

iv) The proportion of participants who experience moderate or more severe pain during treatment, and the proportion of participants who experience moderate or more severe pain during the 16 weeks following treatment will be analysed using descriptive statistics. The median number of days participants experience moderate or more severe pain will also be reported.

v) To facilitate cost-effectiveness analyses comparing the use of imiquimod 5% cream with excision surgery for nodular and superficial basal cell carcinoma (BCC) the cost implications of both interventions will be estimated and synthesised with primary and secondary outcome measures collected in the efficacy study.

The costing study will follow the identify-measure-value paradigm as recommended by guidelines (ref. Drummond M et al. Methods for the economic evaluation of health care programmes, OUP 2005). The full costs of both interventions will be estimated using micro costing for both procedures; follow-up costs will be assessed based on health care utilisation data collected during the study.

The principal cost-effective analysis will be a comparison of the cost per person successfully treated at 3 years (as determined clinically). A secondary cost-effective analysis will present cost per month without recurrence. Bootstrap techniques will be applied to incremental efficacy and cost data, with probability of cost-effectiveness plotted on cost-effectiveness acceptability curves (CEAC). A range of values for the willingness-to-pay for incremental units of efficacy (probability of successful treatment at 3 years or months without recurrence) will be included in the CEAC and link to the separate conjoint analysis that will elicit patient's willingness-to-pay values for marginal changes in various attributes of their treatment.

2.1.1.3 Subgroup analyses

Subgroup analyses will only be undertaken for the primary efficacy variable. The following analyses will be performed:

i) Assessing whether the effectiveness of imiquimod cream in comparison to surgery is different in participants with nodular BCCs and those with superficial BCCs.

ii) Assessing whether the effectiveness of imiquimod cream in comparison to surgery is different in participants with head and neck lesions and those with lesions on other parts of the body (trunk, arm, leg, other areas).

iii) Assessing whether the effectiveness of imiquimod cream in comparison to surgery varies according to size of lesion (≤15 mm diameters vs. >15 mm diameters).

The above subgroup analyses will be performed by the inclusion of an interaction term between treatment group and the appropriate variable for the subgroup analysis e.g. BCC type, to the final statistical model obtained from the main analysis of the primary outcome variable. An interaction will be declared as statistically significant if the P-value for the interaction term is less than 0.1.

For each of the above subgroup analyses, a sensitivity analysis will be performed including and excluding participants with BCCs who were immunosuppressed at baseline (e.g. transplant patients).

The subgroup analysis of primary interest is the first one listed above (assessing the treatment effect by BCC type). This will be a planned confirmatory analysis whereas the remaining subgroup analyses will be exploratory in nature. The results of the explanatory subgroup analyses will be interpreted with caution.

2.1.1.4 Multiple endpoints

No adjustments will be made for multiple endpoints. There is only one primary outcome variable. Secondary outcome variable findings and subgroup analysis findings will be interpreted with caution in view of the number of statistical tests undertaken.

2.1.1.5 Assessing safety

Safety and tolerability data will be summarised by treatment group using descriptive statistics.

2.1.1.6 Assessing compliance

Compliance data will be summarised by treatment group using descriptive statistics.

2.2 Analysis populations

i) Safety set: All participants who receive at least one application of imiquimod cream or surgery. Participants will be analyzed according to the actual treatment received.

ii) Full Analysis set: All randomised participants with a histologically confirmed BCC lesion, who receive at least one application of imiquimod cream or surgery, do not violate the inclusion/exclusion criteria and for whom the outcome of interest is available. Participants will be analyzed according to the treatment to which they were randomised but the exclusion of participants for whom the outcome of interest is not available will mean the analysis will be performed using a modified intention to treat analysis. This set will be as complete and as close as possible to the intention to treat analysis set with minimal and justified exclusion of participants. (Piaggio et al(2006), ICH (E9) (1998)).

iii) Per protocol set: All participants in the Full Analysis set who complied to the protocol and for whom there are no major protocol violations that could interfere with the objectives of the study. Participants with superficial BCCs who have received imiquimod for less than 4 weeks and participants with nodular BCCs who have received imiquimod for less than 8 weeks will be excluded from the per protocol set.

The primary efficacy analysis will be performed using both the Full Analysis Set and the Per Protocol Set of participants. All other efficacy analyses will

use the Full Analysis Set only since it is only the primary outcome for which non-inferiority is hypothesized.

2.3 Protocol Deviations

The number and percentage of protocol deviations will be summarised by treatment group, overall, and by type of deviation. The following types of protocol deviations will be documented:

i) Withdrawals due to ineligibility
ii) Withdrawals due to adverse events
iii) Withdrawals due to loss to follow-up
iv) Withdrawals due to participant death
v) Withdrawals due to participants receiving neither of the study treatments
vi) Treatment failures
vii) Non-compliers who completed the duration of the study (participants who do not follow the full course of imiquimod treatment)
viii) Insufficient exposure to treatment (participants with superficial BCCs who receive imiquimod for fewer than 4 weeks and participants with nodular BCCs who receive imiquimod for fewer than 8 weeks)
ix) Participants who received the wrong study treatment i.e the one to which they were not randomised, or a non-study treatment
x) Participants who used an additional treatment concurrently for the randomised BCC
xi) Participants who chose not to continue, after receiving a full course of treatment

Any other deviations not specified in the list above will also be reported.

2.4 Derived variables.

The following variables will be calculated:

i) The proportion of participants with clinical evidence of "success" at 3 years

Participants will be categorised as either:

a) Successfully treated with no evidence of treatment failure and no sign of recurrence at, or before 3 years post treatment
b) Treated but evidence of treatment failure or recurrence at, or before 3 years post treatment

When uncertainty exists in the clinical assessment of the lesion a biopsy will be taken and participants will then be classified according to histology. This reflects normal clinical practice. Participants who have surgery after imiquimod for possible recurrence/treatment failure will similarly be classified according to histology. Lesions with positive histology will be regarded as treatment failures.

ii) The proportion of participants with clinical evidence of "success" at 1, 2 and 5 years.

These will be calculated in the same way as the above primary outcome measure.

iii) Time to first recurrence

Time to first recurrence will be classified into one of the following 5 categories: "prior to year 1 visit"; "between year 1 visit and year 2 visit"; "between year 2 visit and year 3 visit"; "between year 3 visit and year 5 visit"; "no recurrence prior to year 5 visit".

iv) The proportion of participants with a lesion of excellent or good appearance as determined by the participant at 6 months.

The cosmetic appearance of a participant's lesion is rated by the participant using a five point Likert scale ("Excellent", "Good", "Fair", "Poor", "Very poor"). Participants will then be categorised into one of the following two groups:

a) Participants with a lesion of excellent or good appearance
b) Participants with a lesion of fair, poor or very poor appearance

This classification relates to participants who have their randomised BCC in an area that is visible to them. Participants who cannot see their randomised BCC or have not recorded their rating of cosmetic appearance will be excluded from the analysis.

v) The proportion of participants with a lesion of excellent or good appearance as determined by the participant at 3 years.

The same procedure as described above will be used to categorise participants into one of the above groups according to their rating of the cosmetic appearance of their lesion at 3 years.

vi) The proportion of participants with a lesion of excellent or good appearance as determined by the independent dermatologist at 6 months.

Participants will be categorised using the same approach as described above for the participant's own rating at 6 months.

vii) The proportion of participants with a lesion of excellent or good appearance as determined by the independent dermatologist at 3 years.

Participants will be categorised using the same approach as described above for the participant's own rating at 3 years.

viii) The proportion of participants experiencing a moderate or more severe level of pain on at least one day during the treatment period.

Participants will assess their daily pain during the treatment period (1 day for surgery; 6 weeks (superficial BCCs) or 12 weeks (nodular BCCs) for imiquimod) using a six point Likert scale ("No pain", "Mild", "Mild-Moderate", "Moderate", "Moderate-Severe", "Severe").

Participants will be categorised into one of the following three groups:

a) Participants who experience moderate or more severe pain
b) Participants who experience mild-moderate or less severe pain
c) Participants who experience no pain

ix) The proportion of participants experiencing a moderate or more severe level of pain during the 16 week follow up period after treatment.

Participants will assess their pain using the same method as described above for the treatment period. They will then be categorised into one of the three groups as above.

2.5 Missing data conventions

Primary and secondary outcome measures will be analyzed using a complete case analysis. The number of participants included in each analysis will be reported by treatment group. Sensitivity analyses assuming the worst case scenario (all participants with missing outcome data had a recurrence/treatment failure) and the best case scenario (all participants with missing outcome data were successfully treated) will also be performed for the primary outcome measure.

2.6 Outliers

Potential outliers will be identified by range checks on data entry and subjected to standard query generation and resolution. Initial descriptive analyses will include identification of potential outliers by box and whisker plots. If after additional investigation there is no evidence that these are errors then the analyses will be repeated after winsoring the data to assess the robustness of the results. Winsoring involves replacing extreme values (outliers) with a specified percentile of the data. In this case, data values below the 2^{nd} percentile will be replaced with the 2^{nd} percentile value and data values above the 98^{th} percentile will be replaced with the 98^{th} percentile value.

2.7. Centre effects

Twelve centres participated in the study. Of these, three centres recruited 77% of the study participants (at least 125 participants per centre). The remaining centres recruited no more than 17 participants per centre with the exception of one centre which recruited 62 participants. The nine centres that recruited fewer than 100 participants will be pooled together to form a composite centre. Centre will be adjusted for as a fixed effect using a type III estimator. Heterogeneity between centres will be investigated by the inclusion of a treatment-by-centre interaction term. If there is no evidence of heterogeneity between centres (i.e. the P value for the treatment-by-centre interaction term is greater than 0.1) the treatment-by-centre interaction term will be removed from the model. The pooling together of the small centres will minimize the loss of efficiency of the type III analysis that occurs when there is wide variation between centre sizes (Schwemer(2000)).

2.8. Documentation and other considerations

Copies of the questionnaires that were used to collect the data and instructions on the completion and scoring of these are included in the appendix.

2.9. Software used

Data will be analysed using Stata version 10.1.

2.10. Levels of significance and confidence intervals

Two-sided 98% confidence intervals for all outcomes will be presented. Details of the non-inferiority margin are given in sections 4.2.1. and 4.2.2. This is based on the relative risk whereby the risk of being treated successfully in the imiquimod group is relative to the surgery group. Results will be declared significantly "non-inferior" if the lower 98% confidence interval for the imiquimod effect relative to surgery is greater than the non-inferiority margin.

Greater confidence will be placed on the results if the conclusions from the intention to treat (ITT) and per protocol (PP) analysis are consistent.

2.11. Breaking of blind

Data analysis will remain blinded until all data analysis has been performed and the results have been checked and approved by the Data Monitoring Committee.

3. ANALYSIS OF SUBJECT CHARACTERISTICS

Continuous data that are approximately normally distributed will be summarised in terms of the mean, standard deviation and number of observations. Skewed data will be presented in terms of the median, lower and upper quartiles, minimum, maximum, and number of observations. Categorical data will be summarised in terms of frequency counts and percentages.

3.1. Disposition

The number of participants screened for entry, excluded prior to randomisation (by major reason and overall), the number of participants randomised and the number entering and completing each phase of the study will be summarised by treatment group and overall, using a CONSORT flow chart. The number and percentage of protocol deviations and post-randomisation discontinuations will also be summarised by treatment group, overall and by major reason.

3.2. Baseline

The following participant characteristics will be described by treatment group:

- Age in years
- Sex
- Number (and type (nodular/superficial)) of BCCs at presentation
- Tumour thickness (>3mm/≤3mm)
- Tumour size (longest diameter (mm))
- Site of BCC at presentation (Head and Neck/Other parts of body (i.e. Trunk, Arm, Leg, Other))
- Fitzpatrick skin type (I/II/III/IV/V/VI)
- Family history of skin cancer (Yes/No)
- Childhood sunburn (Yes/No)
- Extent of sun exposure during 3 age ranges: 0-40 years, 40-60 years, ≥60 years (Frequently/Occasionally/Rarely/Never)
- Previous sunbed use (Yes/No)
- Ethnicity (Caucasian/Afro-caribbean/Hispanic/Asian/Other)
- Current Smoker (Yes/No)
- Employment category (SOC2000 categories)
- Immunosuppressed (Yes/No/Don't know)
- Previous BCCs (Yes/No)
- Number of previous BCCs (>3/≤3)
- Other skin cancers (Yes/No)

4. ANALYSIS OF EFFICACY

Analysis will be undertaken on a modified intention to treat basis in that participants will be analysed in the group to which they were randomised regardless of whether they received the intervention or not (see section 2.2 for further details). A per protocol analysis will also be performed for the primary outcome measure.

4.1. Response variables

4.1.1. Primary outcome measure

i) Clinical evidence of "success" (defined as no evidence of treatment failure and absence of any signs of local recurrence) at, or before 3 years as judged by the consultant dermatologist. Participants who subsequently require surgery for poor response or recurrence will be regarded as treatment failures if histology is proven to be positive.

This is a binary variable coded as:

a) 1 for participants who have been successfully treated with no evidence of treatment failure and no sign of recurrence at or before 3 years post treatment;
b) 0 for participants with evidence of treatment failure or those who have a recurrence either at, or before 3 years post treatment.

Participants who die, move away or are lost to follow up before 3 years will be excluded from the main analysis. These participants will be included in the sensitivity analysis as described in section 2.5.

4.1.2. Secondary outcome measures

i) Clinical evidence of success at 1, 2 and 5 years.

These are binary variables. They will be coded in a similar way to the primary outcome variable.

e.g. recurrences at 1 year will be coded as:

a) 1 for participants who have been successfully treated with no evidence of treatment failure and no sign of recurrence at one year post treatment;
b) 0 for participants with evidence of treatment failure or those who have a recurrence at, or before one year post treatment.

ii) Time to first recurrence

This is an ordinal variable with 5 categories: "prior to year 1 visit"; "between year 1 visit and year 2 visit"; "between year 2 visit and year 3 visit"; "between year 3 visit and year 5 visit"; "no recurrence prior to year 5 visit". These categories will be coded as 0,1,2,3,4 respectively.

iii) Cosmetic appearance of lesion site at 6 months and at 3 years as rated by the participant and similarly as rated by the independent dermatologist.

These are binary variables. They will be coded as:

a) 1 for participants with a lesion of excellent or good appearance
b) 0 for participants with a lesion of fair, poor or very poor appearance

iv) Level of pain during the treatment period and during the 16 week follow-up period after treatment

These are categorical variables. They will be coded as:

a) 2 for participants who experience moderate or more severe pain
b) 1 for participants who experience mild-moderate or less severe pain
c) 0 for participants who experience no pain

The number of days participants experience moderate or more severe pain during the treatment period and similarly during the 16 week follow-up

period after treatment are numerical variables. It is unlikely these will follow a Normal distribution.

4.2. Analysis of Response Variables

4.2.1. Non-inferiority margin

The non-inferiority margin is based on a 97% success rate for surgery and a lower 98% confidence boundary of 84% for imiquimod cream. This gives a non-inferiority margin (lower boundary of a 98% CI for the relative difference in effect expressed as a relative risk) of 0.87 (*d*)). This margin was determined by the clinical judgement of the 4 clinicians who sit on the Trial Steering Committee. The non-inferiority margin will only apply to the analysis of the primary outcome for which non-inferiority is hypothesized.

4.2.2. Primary outcome measure

Figure 1 indicates how non-inferiority will be assessed.

The null hypothesis is: H_0:RR(I/S) ≤ δ

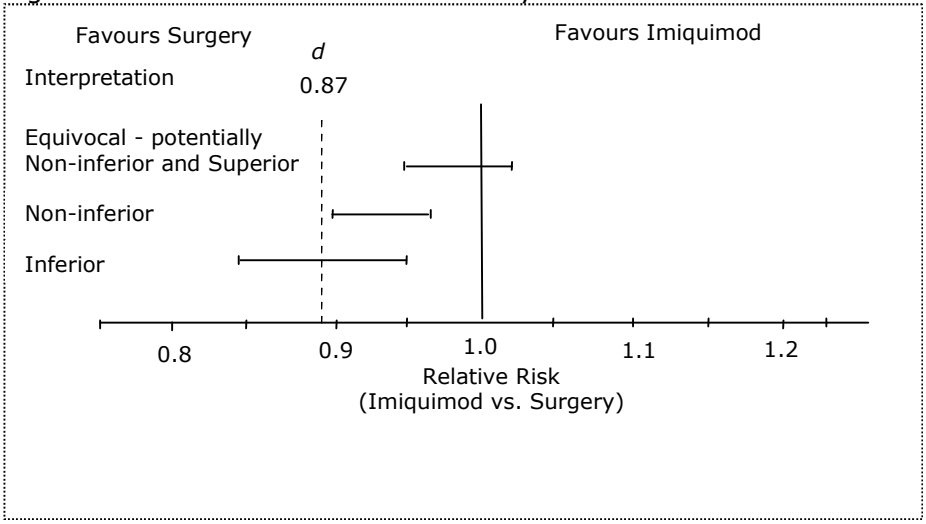
where: RR(I/S) represents the relative risk of imiquimod cream relative to surgery
δ is the noninferiority margin i.e. 0.87

The null hypothesis implies that imiquimod cream is inferior to surgery.

The alternative hypothesis is: H_A: RR(I/S) > δ

The alternative hypothesis implies that imiquimod cream is clinically non-inferior to surgery within the predefined allowable range (δ) of clinical significance.

Figure 1 Assessment on non-inferiority



The number and percentage of participants successfully treated at 3 years (no clinical evidence of treatment failure or a recurrence prior to this time point) in each treatment group, the absolute difference in percentages between groups and the corresponding 98% confidence interval for the absolute difference in percentages will be reported. The number and percentage of participants classified according to histology will be reported by treatment group.

The relative risk will be used to indicate the risk of being treated successfully in the imiquimod group relative to the surgery group. The two-sided 98% confidence interval for the relative risk and the P value obtained from the likelihood ratio test will be presented. Imiquimod will be deemed to be non-inferior to surgery if the results of the intention to treat analysis indicate the lower limit of the 98% CI for the relative risk (imiquimod vs. surgery) is greater than 0.87.

Two separate analyses will be undertaken:

i) Adjusting for centre and tumour type
ii) Adjusting for centre, tumour type, tumour size, tumour site and immunosuppression

4.2.3. Secondary outcome measures

i) Clinical success at 1,2 and 5 years

These will be analysed and presented in the same way as for the primary outcome variable.

ii) Time to first recurrence

The number and percentage of participants in each of the 5 time of first recurrence categories will be reported by treatment group. The odds ratio arising from the continuation ratio model and the corresponding 98% confidence interval will be reported.

iii) Cosmetic appearance of lesion site at 6 months and at 3 years as rated by the participant and similarly as rated by the independent dermatologist

The analysis of primary interest will be the participants rating at 6 months. This will focus on lesion areas visible to the participants (head and neck) and then on all sites. The analysis of the dermatologist's ratings will similarly be based on lesions visible to the participants and then on all sites.

For each of the cosmetic appearance outcome measures, the number and percentage of participants with a lesion of excellent or good appearance in each treatment group, the absolute difference in percentages between groups and the corresponding 98% confidence interval for the absolute difference in percentages will be reported.

The relative risk will be used to indicate the risk of having a lesion of excellent or good appearance in the imiquimod group relative to the surgery group. The two-sided 98% confidence interval for the relative risk and the P value obtained from the likelihood ratio test will be presented.

The inclusion of baseline variables in the model to assess the robustness of the findings will be performed using the same approach as for the primary outcome measure (section 4.2.2). A third model will also be fitted. This will adjust for smoking (current smoker (Yes/No)) in addition to the variables specified in the second model for the primary outcome measure in section 4.2.2 (centre, tumour type, tumour size, tumour site and immunosuppression).

iv) Level of pain rated during the treatment period and during the 16 week follow-up period after treatment

For each of these outcome measures, the number and percentage of participants who fall into each of the categories outlined in section 4.1.2 will be reported by group. The median (lower and upper quartiles, and minimum and maximum) number of days that participants experience pain will also be reported by group.

4.2.4. Other analyses

The following indicators of treatment compliance in the imiquimod group will be reported:

i) The number and percentage of participants who had sufficient exposure (as defined in section 1.9) and comply with the instructions for using imiquimod cream.
ii) The number and percentage of participants who had an agreed break in the treatment course as recorded on the dose change form.
iii) The number of agreed breaks recorded on the dose change form during the participant's course of treatment.
iv) The number and percentage of participants who did not have an agreed break and did not receive the full treatment course because they did not comply with the instructions for using imiquimod cream.

5. ANALYSIS OF SAFETY & TOLERABILITY

Participants will be analysed according to the treatment they received.

5.1. Exposure to imiquimod cream

Participants are supplied with one sachet of imiquimod cream per treatment day. The amount of imiquimod cream used by participants will be estimated from the diary where participants indicate on a daily basis whether they have applied the cream.

The number of days of exposure to imiquimod cream will be summarised using the mean and standard deviation, if the data are approximately normally distributed or using the median, lower and upper quartiles, minimum, maximum and number of observations, if the data are skewed.

The number and percentage of participants who fall into the following categories will also be reported:

i) Patients who had insufficient exposure to imiquimod cream (<4 weeks treatment for superficial BCCs; <8 weeks treatment for nodular BCCs).
ii) Patients who were unable to complete the full course of imiquimod treatment as result of a treatment related adverse event.
iii) Patients who were unable to complete the full course of imiquimod treatment as result of a non-treatment related adverse event.

5.2. Adverse events

Adverse event summaries will be based upon the number of participants reporting adverse events and the number of events reported per participant. They will be reported by treatment group and BCC type.

The following summary tables will be produced:

- Occurrence of adverse event in first 6 months from start of treatment

- Occurrence of possibly treatment related adverse event in first 6 months from start of treatment
- Occurrence of adverse event throughout the duration of the trial
- Occurrence of possibly treatment related adverse event throughout the duration of the trial
- Occurrence of serious adverse events
- Reason why serious adverse events were considered to be serious
- Severity of adverse events
- Adverse events leading to withdrawals, or for which medication was taken, or resulting in a change of imiquimod dose
- Number of days of itching of the randomised BCC during and in the 16 weeks after treatment
- Number of days of weeping of the randomised BCC during and in the 16 weeks after treatment

5.3. Safety listings

The following listings will be included in the Appendix.

5.3.1 Exposure to imiquimod

The number of days of exposure to imiquimod cream, an indicator of whether this was sufficient (yes/no) and tumour type will be listed by participant.

5.3.2 Adverse event details

Adverse events will be listed by participant. The following information will be included:

- Type of adverse event
- Day adverse event started (number of days from the start of study treatment)
- Duration of the adverse event
- Severity of the adverse event
- Whether the adverse event could be related to the study treatment

5.3.3 Weeping and Itching

For all participants, the number of days they record weeping and itching of the randomised BCC occurred will be listed by participant.

6. LIST OF PROPOSED SUMMARY TABLES
   - 6.1. Flow diagram of participant flow with details of eligibility, number randomised, withdrawals, loses to follow up, exclusions and number analysed
   - 6.2. Baseline characteristics of participants
   - 6.3. Current medical condition at baseline
   - 6.4. Baseline response variables
   - 6.5. Primary outcome measure: clinical evidence of success at 3 years
   - 6.6. Secondary outcome measures:
     - 6.6.1. Clinical evidence of success at 1,2 and 5 years
     - 6.6.2. Time to first recurrence
     - 6.6.3. Cosmetic appearance as rated by the participant and independent assessor at 6 months and at 3 years
     - 6.6.4. Level of pain as reported by the participant during the treatment period and during the 16 week follow up period after treatment
     - 6.6.5. Cost effectiveness
   - 6.7. Details of compliance for participants in the imiquimod group
   - 6.8. Safety and tolerability details

7. LIST OF APPENDICES
   7.1. Listings
   7.2. Adverse events
      7.2.1. All adverse events (including non-treatment-emergent events) by patient, centre, age, sex, race, adverse event (body system, preferred term, reported term), number of days since start of treatment, number of days since onset of adverse event, duration, severity, seriousness, action taken, outcome and causality. by-patient listing of all serious adverse events
      7.2.2. by-patient listing of all adverse events leading to withdrawal
      7.2.3. by-patient listing of all deaths that occurred during the study
   7.3. Data collection questionnaires

8. REFERENCES

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