CRC CLINICAL TRIALS

CONFIDENTIAL

FINAL STUDY PROTOCOL

A RANDOMISED CONTROLLED TRIAL OF EXCISIONAL SURGERY VERSUS IMIQUIMOD 5% CREAM FOR NODULAR AND SUPERFICIAL BASAL CELL CARCINOMA

Dr. Fiona Bath-Hextall and Professor Hywel Williams,

Centre for Evidence-Based Dermatology,
Queens Medical Centre,
Nottingham NG7 2UH

Tel: 0115 82 31048
Fax: 0115 82 31046

e-mail: fiona.bath-hextall@nottingham.ac.uk and hywel.williams@nottingham.ac.uk

Signature Page:

I agree to conduct this trial in accordance with the requirements of the protocol and also in accordance with the following:

- **Declaration of Helsinki (latest version)**
- **GCP of the European Community, CPMP/ICH/135/95**
- **Respective local laws and regulations**
- **Regulatory requirements for reporting Serious Adverse Events**

Signatures:

Principal Investigators:

1. Dr William Perkins _____
2. Dr Graham Colver _____
3. Dr Irshad Zaki _____
4. Dr Jan Bong _____
5. Dr Robert Herd _____
6. Dr Clare Fitzsimons _____
7. Dr Simon Tucker _____
8. Dr Khalid Hussain _____
9. Dr Girish Gupta _____
10. Dr Graham Sharpe _____
11. Dr Catherine Harwood _____
12. Dr Camilo Diaz _____

PROF HYWEL WILLIAMS

Chief Investigator Name	**Date**	**Signature:**

Contents:

Abbreviations

BCC = basal cell carcinoma

sBCC = superficial basal cell carcinoma

nBCC = nodular basal cell carcinoma

RCT = randomised controlled clinical trial

1. Full title of trial
A RANDOMISED CONTROLLED TRIAL OF EXCISIONAL SURGERY VERSUS IMIQUIMOD 5% CREAM FOR NODULAR AND SUPERFICIAL BASAL CELL CARCINOMA

1.1 Acronym
SINS (**S**urgery versus **I**miquimod for **N**odular and **S**uperficial basal cell carcinoma)

1.2 Contact applicant
Dr Fiona Bath-Hextall (formerly Bath), PhD, Centre of Evidence-Based Dermatology, C Floor, South Block, Queens Medical Centre, Nottingham NG7 2UH
Tel 0115 82 (30884), mobile 07811 737679
e-mail fiona.bath-hextall@nottingham.ac.uk

1.3 Planned starting and closing date
Original planned dates (for the grant to run) were March 2002 to March 2007. Actual start date (start of funding) was 16th September 2002. The last patient visit will be 3 years after the last person is randomised (current aim - 2006 - is to finish recruitment end of October 2006), with postal follow-up of records at 5 years (end of 2011), followed by final analysis. Actual end of recruitment was 22nd February 2007.

2 The need for a trial

Since this study was started, there have been two major publications (See Rhodes et al. Five year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. Arch Dermatol. 2007; 143(9):1131-1136 and Bath-Hextall FJ, Perkins W, Bong J, Williams HC. Interventions for basal cell carcinoma of the skin. Cochrane Database of Systematic Reviews 2007, Issue 1. and Cochrane review) as well as other more minor publications, but the content of these have not affected the design or conduct of the study.

2.1 What is the problem to be addressed?
Incidence and causes
Basal cell carcinoma (BCC) is the most common malignant tumour in humans[1, 2, 3]. Over 30,000 new cases are reported each year in the UK. This is likely to be an underestimate due to inconsistencies in registration of basal cell carcinomas at Regional Cancer Registries[4]. The tumour may occur at any age but the incidence of BCC increases markedly after the age of 40. The incidence of BCC appears to be increasing in younger people, probably as a result of increased sun exposure[5]. The incidence rate (standardised using the European standard population) for new BCCs in the Trent Cancer Registry increased from 36.8 in 1985 to 71.3 for men and from 25.6 to 52.0 in women (data kindly provided by Trent Cancer Registry, September 2001). A total of 3,826 new BCCs were registered in Trent in 2000 (80% of all non-melanoma skin cancers). A sustained rise in the incidence of BCC has been documented using a validated register in South Wales[6]. Reliable national figures for BCC incidence are impossible to obtain because some cancer registries in the UK do not register BCCs. In America, the incidence of BCC has doubled approximately every 14 years[7] and similar changes have occurred in Australia[8].

Risk factors include a fair skin, red hair, blue eyes, Celtic ancestry, tendency to freckle[9], male sex and degree of sun exposure[10, 11, 12, 13]. The attributable risk owing to host factor variables is low, because most BCC patients do not have identifiable phenotypic markers of high risk[14]. Both familial basal cell carcinoma syndrome (Gorlin's syndrome) and sporadic forms have been associated with Patched gene mutations, which probably act through the sonic hedgehog signalling pathway[15, 16, 17]. Others have found that people who present with a cluster of new BCCs or truncal BCCs may have abnormal genetic pathways associated with

glutathione S-transferase and the cytochrome P450 pathways[18]. More details on the possible genetic-environment interaction are provided in the genetic markers project addendum.

Clinical variants

Clinical appearances and morphology are diverse. These include nodular, cystic, ulcerated (rodent ulcer), superficial, morphoeic (scarring), keratotic and pigmented variants. Nodular BCC is the most common type (60 to 85%). In a recent audit of 159 basal cell carcinomas excised at Queen's Medical Centre, 21 (12%) were classified as superficial, 139 (78%) as nodular and 19 (11%) morphoeic. Eighty-five percent of all BCCs appear on the head and neck region[19, 20], ie visible areas where a good cosmetic and functional result is important.

BCC growth and its predictors

Growth of BCC is a localised phenomenon in people with a competent immune system. BCCs tend to infiltrate surrounding tissues in a three-dimensional fashion through the irregular extension of finger-like outgrowths which may not be apparent clinically[21, 2]. If left untreated, or if they are inadequately treated, the BCC can cause extensive local tissue destruction, particularly on the face. Neglected cases may even infiltrate bone and deeper structures such as the brain and cause death[22]. Death from BCC is extremely rare, but may occur in neglected cases and/or in those with major underlying immunosuppression. The clinical course of BCC is unpredictable. It can remain small for years with little tendency to grow, it may grow rapidly, or it may proceed by successive spurts of extension of tumour and partial regression[23]. Histological subtype (infiltrative, micronodular or morphoeic patterns), initial diameter and male sex have recently been shown to be the best independent predictors of BCC invasion[24]. It is unknown whether the phenotypic characterstics of people who present with clusters of BCCs or those who develop BCCs on truncal sites are also associated with increased growth once a BCC has established. It is unknown if treatment response to an agent such as imiquimod is associated with polymorphisms in genes involved in these clustered/truncal phenotypes or whether other genes responsible for immune surveillance may be important. This is the rationale for the added molecular markers for the treatment response study in collaboration with Professor Strange's team at Stoke-on-Trent (see molecular study addendum).

Current treatments

The current first line treatment of BCC is usually surgical excision by means of day case surgery. Numerous alternatives are available and include: curettage and cautery, cryosurgery, laser ablation, excision with various predetermined margins, excision under frozen section control (Moh's micrographic surgery), radiotherapy, topical therapy with 5-fluorouracil, intralesional therapies such as interferon, photodynamic therapy, and systemic chemotherapy. Surgical treatment, considered the gold standard (around 95 to 98% success rate), requires trained staff and access to a suitably equipped operating theatre[3, 25, 26]. Some degree of discomfort is common during and after BCC excision, and the cosmetic and functional may be compromised by scarring. Treatment of people with multiple BCCs can be particularly problematic. Other techniques are time consuming for the specialist and patient, they may be quite painful (eg cryotherapy), they may be less effective (curettage and cautery) and they may need several hospital visits (eg radiotherapy). Some recent interest has been shown in the use of photodynamic therapy (PDT), yet success rates at 1-year were 75% at best in the PDT and many patients had to undergo two or three treatments[27].

Why a home-use cream could be useful

A topical treatment with acceptable success rates and low side effects, which is amenable to easy home application, might offer an alternative and cost-effective way of dealing with at least some of the people with BCCs that contribute to the heavy work load for current health services. Even if, as we anticipate, such a treatment is less effective than surgery, it might still prove to be useful and cost effective in public health terms for this non-life threatening tumour. Any recurrences or failure of the cream in low-risk sites (such as the trunk, limbs, neck and some areas of the face) can easily be recognised and then dealt with surgically.

The current UK workload crisis for BCC

Much of the increase in workload for dermatologists in the UK over recent years is due to an increase in solar-induced skin cancers and suspected cancers within an increasingly ageing population[28]. The increasing number of BCCs in younger people suggests a cohort effect from excessive cumulative sun exposure and points to a problem that it is likely to become much larger before the benefits of sun avoidance in successive generations takes hold. The current complement of 348 UK dermatologists are already experiencing difficulties in dealing with the large increase in skin cancer surgery[29], especially with the imposition of the new two week wait for suspected skin cancer. The effects of an increasingly ageing population, cohort effects from previous leisure sun exposure, increased public awareness of skin cancer and increased surveillance of prevalent cases by primary care teams are all likely to conspire to worsen the current crisis in dealing with basal cell carcinoma in the UK, and in other countries such as Australia.

Preliminary clinical evidence of imiquimod for BCC

Imiquimod is an immune response modifier that has been shown to induce cytokines that promote a TH1 lymphocyte or cell-mediated immune response[30, 31, 32]. These include interferon alfa (IFN-α), IFN-λ, and interleukin 12 (IL-12). In animal studies, imiquimod has demonstrated broad antiviral and anti-tumour effects that are largely mediated by IFN-α[31]. In humans, imiquimod 5% cream has been demonstrated to be safe and effective in the treatment of external anogenital warts[33, 34, 35].

One study of 35 patients has evaluated the safety and efficacy of imiquimod 5% cream in the treatment of superficial and nodular BCC[36, 37]. This small trial suggested success rates similar to those of excisional surgery with the added advantage of no scarring. Another phase II dose response trial of imiquimod 5% cream applied for 6 weeks in 99 Australian patients with primary superficial BCC found 100% histological clearance in a twice daily regimen (3/3), a 88% clearance in a once-daily regimen (29/33), a 73% clearance (22/30) in the 6 times a week regimen and a 70% clearance (23/33) for those treated 3 times a week[38]. Clearance was defined as patients with no histological evidence of BCC when the site of the treated lesion was excised 6 weeks after imiquimod treatment. This study was important as it suggested that the once daily regimen appeared to be the best compromise between efficacy and minor side effects such as soreness and redness at the site of application. Another similar multi-centre RCT of 129 patients with superficial BCC compared imiquimod twice daily, once daily, 5 days per week or 3 days per week versus vehicle using the same end-points[39]. Intention-to-treat analysis showed clearance rates of 100% (10/10), 87% (27/31), 81% (21/26) and 52% for the twice daily, once-daily, 5 days a week and 3 days/week groups respectively. Interestingly, there was a small vehicle response rate of 19% (6/32). Another study of patients with superficial BCC found that occlusion increased the success rate for thrice weekly application of imiquimod from 76% (19/25) to 87% (20/23)[40].

Two further industry-sponsored trials conducted in Australia and the US have evaluated 5% imiquimod cream for the treatment of nodular basal cell carcinoma. One of these studies reported histological clearance rates of 71% (25/35) for once-daily treatment for 6 weeks[41]. Another vehicle-controlled RCT of 92 patients with nodular BCC who underwent treatment for 12 weeks using twice daily, once daily, 5 days a week or 3 days a week reported intention-to-treat histological clearance rates of 75% (3/4), 76% (16/21), 70% (16/23) and 60% (12/20) for the four groups respectively, with a vehicle response rate of 13% (3/24)[42]. This study suggested that longer treatment times (ie 12 weeks as opposed to 6 weeks) are needed to treat nodular tumours. This is what one might anticipate from a treatment that relies on percutaneous penetration ie tumour depth may be an important predictor of treatment response.

In all of these trials patients were themselves able to apply the cream, thus allowing the dermatologists more time to concentrate on the high risk BCCs. The trials were both short-term, using histological evidence of residual BCC in excision specimens as a surrogate for longer-term clinical recurrence.

Collectively, these preliminary phase II studies suggest a high success rate (87 to 88%) for imiquimod for treating superficial BCC using a once-daily regimen for 6 weeks and a useful (76%) treatment response when treating nodular BCC for 12 weeks. It is therefore timely to carry out a full scale and definitive randomised controlled trial (RCT) of imiquimod 5% cream versus the best treatment currently available (surgery), to determine if acceptable long-term clinical success rates can be achieved with good or better cosmetic and functional results. If successful, this treatment would have the added convenience of home treatment for the common type of uncomplicated low-risk BCCs, which constitute the bulk of the workload for most dermatology departments. We believe that a separate trial for high-risk areas (such as near the eye) may be required at a later date, as these may require different treatment approaches.

2.2 What are the hypotheses to be tested?

1. 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?
2. Is imiquimod more cost effective than surgery for low-risk BCC?
3. Does imiquimod result in a more aesthetically acceptable result than conventional excision?
4. Do certain phenotypic features and gene polymorphisms predict tumour responsiveness to treatment?

2.3 Why is a trial needed now?

The recent NHS Service Framework on cancer services states that by the year 2000, patients with any suspected squamous cell carcinoma or malignant melanoma are expected to be seen by a specialist within 2 weeks[43]. Referral guidelines suggest that raised, growing and ulcerated lesions should be referred - a description that also refers to the much more common BCCs. Although some units have not included basal cell carcinoma in this 2-week wait scheme, preliminary work at the Nottingham unit suggests that excluding BCC is unwise because melanomas might be missed in those lesions provisionally diagnosed as basal cell carcinoma by the general practitioner[44]. It is for this reason that our skin cancer team and many others include all forms of suspected skin cancer in their 2-week wait deadline.

Implementation of this maximum 2-week wait for skin cancer is already placing a significant extra workload on dermatology departments in the UK, often at the expense of people with serious and debilitating inflammatory skin disorders who inevitably have to wait longer to be assessed. With an increasing incidence of skin cancer, it is therefore desirable to have a pragmatic and reliable treatment for BCC that is pleasing for the patient, giving a good cosmetic result with as little distress as possible in terms of pain and number of hospital visits. In evaluating such new therapies, any loss of efficacy when compared with conventional surgery needs to be traded against the possible gains in cosmetic result, and cost benefits that might result from saved surgical procedures. The limited number of UK dermatologists will then be able to spend their time more efficiently by dealing with more complicated high risk cases and recurrences or use their limited time dealing with urgent inflammatory skin diseases which might have been sidelined with the new cancer treatment directives.

A trial is needed now as the pilot studies to date have not compared the new technology to a suitable standard comparator (surgery). This trial is crucial in order to understand the relative cost-effectiveness of such treatment alternatives. A less effective but acceptable treatment may still prove to be highly cost effective when used in series (as opposed to parallel) with excisional surgery, since surgery can easily be performed promptly to deal with any subsequent treatment failures.

It is also important to note that longer-term follow-up (ie years) is needed to catch late recurrences of slower-growing tumours. Previous RCTs on imiquimod cream have been too short to provide useful data for informing patient and physician choice. It is also unclear whether the short-term histological clearance

reported in the Phase II studies can be translated into a durable clinical clearance. Also, the Phase II studies published to date suggest a gradient of treatment response depending on the histological subtype. More precise estimates of treatment efficacy using much larger sample sizes are needed for the commoner nodular BCC. Whilst this could be done through industry-sponsored phase III trials, it is important to have a definitive independent trial with cost-effectiveness data and long term follow up in order to inform the patients, health care workers and the NHS of what might be a major new way of managing BCC.

Some information on possible predictors (clinical and genetic) of treatment response that might be possible to explore in a large study such as ours might also be useful for guiding clinical practice. At present, imiquimod cream is not used routinely for BCC in clinical practice, and clinical opinion is divided regarding its potential usefulness for different types of BCC. It is thus timely to consider a trial given such clinical equipoise. Without such a trial, it is likely that the technology may become assimilated without adequate evaluation. If imiquimod is less effective than the pilot studies suggest, this could result in unnecessary suffering from inadequate treatment on a large scale. Conversely, if it is more effective for nodular BCC than the preliminary studies have suggested, then it may be more widely adopted in health care services.

In summary, the *timeliness* of this trial is supported by:
1. The clinical service for BCC is in crisis
2. Pilot studies have not compared imiquimod against standard best practice (ie surgical removal)
3. No data on cost-effectiveness is available to inform service developments
4. It is unclear if histological clearance following imiquimod described in the pilot studies can be translated to long-term clinical clearance
5. More precise estimates of treatment efficacy are needed especially for nodular BCC
6. Current clinical equipoise on the use of imiquimod for BCC
7. The trial provides an opportunity to identify possible genetic predictors of treatment response

2.4 Has a systematic review been carried out and what were the findings?
One systematic review on treatment modalities for basal cell carcinoma has been published in 1999[26]. The authors limited their analyses to 18 English language studies published after 1970 which dealt with a total of 9930 BCCs followed for 5 years. For each of the five commonest treatment modalities, recurrence rates were less than 10%. The main drawback of that review was that most of the included studies were not randomised controlled clinical trials. This increases the problems in combining data which are not truly comparable. The authors concluded their review, however, with a strong plea for long-term RCTs in the area of BCC treatment, a view that was echoed in an accompanying editorial[45].

We are in the process of conducting a Cochrane systematic review under the auspices of the Cochrane Skin Group. The protocol has been refereed and is now due for publishing on the next version of the *Cochrane Library*. The process of doing a full Cochrane review for this subject is likely to take a further 12 months, so two of the team members have already done a preliminary review of the data according to the protocol. This entailed searches performed by the Cochrane Skin Group's trial search co-ordinator (Finola Delamere) which included the Skin Group's specialised register, the Cochrane Controlled Clinical Trials Register, Medline, EmBase and the National Research Register. It is the most comprehensive attempt to identify all relevant published and ongoing randomised controlled trials of interventions in basal cell carcinoma to date.

Fourteen published randomised controlled trials (RCTs) with very different protocols were identified. One of these was excluded on the grounds that the BCCs were not biopsy proven. Another five abstracts and four ongoing trials have been identified. The review highlights the severe lack of RCTs in such an important area. The included trials followed up patients for BCC recurrence for months rather than years. This is important, as clinical success rates measured at 1 year may be associated with residual tumour that is only visible on full histological examination. Such tumours would be likely to recur within a 3 to 5 year period, yielding more

pessimistic success rate estimates[27]. Our review suggests that long follow up rates (ie 3 to 5 years) are key in determining whether treatments simply mask the superficial clinical signs of tumours which then continue to spread beneath the skin surface. Since most evidence suggests that the majority of BCCs which recur will present within 3 years of treatment[46] these trials do not give a clear idea of the true effectiveness of the treatments tested. There were no RCT's comparing surgery versus no surgery. One trial compared surgery versus radiotherapy, including BCC in high and low risk areas. Surgery was significantly better than radiotherapy in this study. Similar results were shown in an RCT of radiotherapy versus surgery for BCC of the face, with significantly poorer cosmetic outcome for the radiotherapy group[47].

It is a paradox that the most common cancer in humans has been studied by the least number of RCTs. Those trials that have been done have generally been of poor quality and short duration. This probably reflects the lack of industry and independent investment into researching this area.

2.5 How will the results of this trial be used?

If imiquimod 5% cream turns out to have an acceptable success rate, is cost-effective and easy to use, then it could become an effective treatment option for the routine first treatment for the majority of low risk nodular and superficial BCCs seen in skin cancer clinics in the UK and elsewhere. Recurrences and high risk BCCs could then be dealt with surgically by dermatologists and plastic surgeons working as part of the newly set up skin cancer teams. *Such an approach would represent a paradigm shift in the management of BCCs*, placing more emphasis on patient involvement and community treatment for the majority of lesions. If the 90% efficacy for superficial BCCs suggested in the pilot studies is confirmed in this study, then imiquimod might be *preferable* to surgery (around 95% efficacy) because of the better cosmetic result.

It could also be conceived that treatment with imiquimod could start in the community after the diagnosis of BCC has been proven by a small diagnostic biopsy or cytology. Care would need to be taken through appropriate Medical College guidelines to ensure that the use of such a preparation in the community is implemented through a strict protocol, which requires a confirmatory diagnostic biopsy beforehand. This would mitigate against the situation of the cream being used indiscriminately for all non-healing lesions – a practice that might drastically increase costs to the NHS given the number of lesions that could be mistaken for a BCC (eg actinic keratoses) in general practice. At a more serious level, indiscriminate use of imiquimod for all non-healing lesions could promote diagnostic uncertainty and delay in diagnosing some melanomas.

In summary:

i) For *large* (greater than 4cm diameter) superficial BCCs, an efficacy of around 90% might make imiquimod the treatment of choice because of better cosmetic results despite being slightly inferior to excisional surgery

ii) For smaller superficial BCCs, an efficacy of around 90% would still make it a more attractive option to non-surgical treatments with similar efficacy such as cryotherapy or curettage because it can be used at home

iii) Efficacy rates of as low as 70% for nodular BCC at low-risk sites could still be useful and cost-effective for dealing with the bulk of BCCs. These are non life-threatening lesions which can be dealt with surgically if recurrences occur at low-risk sites. In other words, a “treat with the cream first and see what’s left policy” might become a viable and more cost effective future treatment option.

2.6 Please detail any risks to the safety of participants involved in the trial

Normal risk for excisional surgery (bleeding, wound infection, pain). We are unaware of any rare serious risks to participants using topical imiquimod cream (please see Summary of Product Characteristics sheet). However, most participants would experience some degree of redness and/or soreness of the skin with use of the cream. This inflammatory reaction may be an important part of the local immune response. This situation is already encountered in clinical practice through the use of topical 5-fluouracil for the treatment of actinic

keratoses, and is rarely severe enough to warrant stopping treatment. Data from the study[38] on superficial BCC suggested that twice daily application of imiquimod was associated with too much soreness/burning – hence the choice of once daily treatment in this study.

3 The proposed trial

3.1 What is the proposed trial design?

Prospective, multi-centre (initially three), randomised controlled phase III trial, to compare excision surgery and imiquimod cream for nodular and superficial basal cell carcinoma presenting in low risk areas. Low risk area as defined in "The British Association Dermatology Guidelines for the management of basal cell carcinoma"[3].

3.2 What are the planned trial interventions?

A punch or shave biopsy specimen of no more than 25% of the total lesion to confirm diagnosis of BCC before randomisation to either:

1. Imiquimod 5% cream once daily for 6 (superficial) or 12 (nodular) weeks total, or
2. Surgical excision with a 4mm margin

We are aware that the manufacturers of imiquimod are about to report the results of another large dose-finding clinical study in late Spring 2002 where optimum frequency of dosage is being explored for superficial BCC (eg once daily for 7 days versus five times a week). If those studies suggest that a particular protocol such as five times weekly is optimal in terms of risk/benefit, then we would consider changing to this after consultation with the CRC, especially if this frequency became the basis of the drug licence for treatment of superficial BCC. We would of course inform the local ethics committees of such a change.
Note: We met with the manufacturers and results did not result in changing our planned once a day dosing.

In order to identify possible genetic markers for tumour response, 5ml of blood will also be taken from participants consenting to take part in the study at the study outset. This will be placed in EDTA containing tubes. Methods for analysing the genetic marker data are given in the addendum.

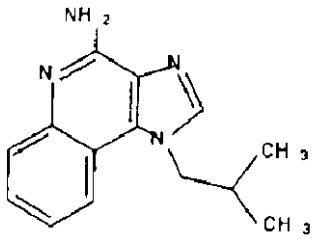
The intervention:

Chemical name: 1-(2-methylpropyl)- 1H-imidazo-{4,5-c}quinolin-4-amine

Trade name: Aldara 5% cream

Qualitative and Quantitative Composition: Imiquimod 5mg per 100 mg cream. Each sachet contains 12.5 mg of imiquimod

Chemical Structure:



Should we include other treatment arms?
We have debated whether to include other trial arms in this study. We considered the use of a placebo cream unethical in such a Phase III study. Although the act of initial diagnostic biopsy might incite an inflammatory reaction sufficient to "cure" some superficial BCC lesions, this effect is unlikely to be clinically useful by itself. It is acknowledged however that *some* of the benefit of topical imiquimod might be due in part to the procedure of diagnostic biopsy. Since this is what would happen in real clinical practice were the intervention to be adopted more widely (ie diagnostic biopsy plus cream), this would not matter from the pragmatic point of view.

It is also tempting to include other treatment modalities such as cryotherapy or curettage – treatment modalities with "cure" rates of 90% or less which may be considered "fair comparators" for imiquimod. None of the other treatments are universally accepted to be as effective as surgery, and there is large variation in their usage and consequent "cure" rates. For example, a recent audit of treatment of BCC using currettage and cautery at Sheffield suggested a 5-year success rate of only 70%, perhaps due to suboptimal technique[48]. It is our philosophy to keep this study as simple as possible by comparing the new technology against the best existing treatment ie excision surgery in a pragmatic way which will help to inform future clinical practice.

3.3 What is the proposed duration of treatment period?
The treatment period for the imiquimod cream group will be 6 (superficial) or 12 (nodular) weeks. The surgical group will be operated on as soon as local conditions permit (normally anything from immediate surgery to four weeks depending on prioritisation according to patient's risk, social circumstances and surgical waiting lists).

Justification: The Marks et al 2001[38] study suggested that a once-daily 6-week treatment period was optimal for *superficial* BCC. Little gain seems to be seen if treatment is extended to 12 weeks for such lesions[39]. The Phase II trials on *nodular* BCC studies suggested that histological clearance rates increase from 71% to 76% when 12 as opposed to 6 weeks treatment is used. We therefore propose that the consultant dermatologist will decide if the lesion is superficial or nodular at the study outset (this can be confirmed by the diagnostic biopsy result around two weeks later). If the lesion is superficial, then the treatment period will be once daily for 6 weeks. If the lesion is nodular, then the treatment period will be once daily for 12 weeks. This is likely to reflect what would happen in real life were the treatment to become available. Treatment failures (after either a biopsy or a period of watchful waiting) will be treated by surgical excision.

It seems sensible on the basis of existing studies to specify a treatment period of 6 weeks for superficial BCC and 12 weeks for nodular BCC. Despite the possible gains of even higher success rates with treatment periods of longer than 12 weeks, it seems unreasonable to expect participants to continue a once-daily cream application for more than 12 weeks in this study, plus the difficulties of BCC assessment while there is substantial skin irritation make it difficult to treat for "as long as is needed".

3.4 What are the planned inclusion /exclusion criteria?
These are as broad and inclusive as possible in order to approximate the sort of patients encountered outside the usual strict clinical trial environment in order to improve external validity.

Inclusion criteria
- Men and women of any age who present clinically with either primary nodular or superficial BCCs, or a skin lesion other than BCC which turns out on histology to be a superficial or nodular BCC.
- Any number of BCCs (although only one per participant is selected for the study)
- Histologically proven BCC

- Location of primary nodular/superficial BCC in low risk areas (it is difficult to justify using imiquimod to areas at high risk of recurrence such as those situated near the embryological fusion lines of the face where delay of appropriate surgery might result in more invasive procedures)
- Informed consent
- Must have access to a telephone

Exclusion Criteria

- Genetic or nevoid conditions such as Gorlin's syndrome
- Morphoeic (microinfiltrative) trial lesion as diagnosed clinically (even if not histologically classed as morphoeic – histological sample may have missed infiltrative nature of lesion)
- Allergy to any of the interventions
- Involvement in a trial of another experimental intervention
- Life threatening disease
- Patients with bleeding disorders
- Patients not available for follow up for 3 yrs (eg patients with no fixed address or overseas visitors)
- Pregnant, intention to become pregnant during treatment phase of the trial, or breastfeeding (such patients would be offered normal surgery)

We do not plan to exclude immunosuppressed patients eg those on cyclosporin for renal transplants, on the basis that they contribute to around 10% of the BCC workload. Whilst it is true that they may exhibit different treatment responses because of decreased immunosurveillance, we do not know this for sure. We propose to include them as typical of the patients with BCC that we see everyday and to then perform a sensitivity analysis including and excluding such patients to see if it alter the study conclusions.

3.5 What are the proposed outcome measures?

Primary – Clinical evidence of "success" (defined as absence of any signs of local recurrence) at 3 years as judged by the consultant dermatologist looking after that participant. Participants allocated cream who subsequently require surgery for poor response or recurrence will be counted as treatment failures.

Secondary –

i) Recurrences at one, two and five years. If recurrences occur, complete excision of the lesion to be performed**,** once biopsy results are obtained or after a period of watchful waiting
ii) Time to first recurrence
iii) Aesthetic appearance of lesion site to be scored by the participant and blinded observer independently at all follow up times (from six months) using a five point Likert scale.
iv) Pain will be assessed by a pain questionnaire using a six-point scale filled in at home to assess pain a) during treatment and b) in the 16 weeks following treatment.
v) Cost effectiveness for the different treatment modalities to include number of participant visits to hospital, as well as cost of treatment per session.

Justification of primary outcome measure: We have debated whether a further biopsy (incisional or excisional) is needed at 3 years to confirm the clinical clearance. The advantage of such a biopsy would be that the main assessment by a histopathologist could then be blinded to intervention status. We have decided against this because a) this is not what would happen in clinical practice and b) participants who have benefited from an excellent cosmetic result in the cream group are unlikely to want to have a scar from a biopsy since avoidance of a scar was a perceived benefit of entering the study. There is likely to be considerable sampling error in taking incisional and even excisional biopsies after a 3-year period given the variation in skin laxity in relation to bony landmarks in this age group even on a week to week basis. Tattooing the skin to denote the original lesion seems an unpleasant intervention for participants that might

seriously worsen recruitment. It is also questionable how blinded a histopathologist would really be as there would be signs of previous surgical scar tissue in those who had undergone surgical excision initially.

We have also chosen against using early complete histopathological excision as a surrogate measure of long-term success (eg 6 weeks after treatment as in the Phase II studies) as the validity of such a surrogate is not known. It is interesting to note that even application of a vehicle cream was associated with a 1% histopathological clearance in the Phase II studies. Whilst this could be as a result of a genuine non-specific inflammatory effect, missing small collections of BCC cells between successive histopathological block sections could be another.

We acknowledge that the concept of "cure" at 3 years might be a fallacy for BCC. The longer BCC patients have been followed, the higher the recurrence rates[46]. We prefer therefore to use the term "success" rates at various time points and to include at least one long term (5-year) surveillance for late recurrences by surveying GP and hospital records. This will be done in accordance with the Caldicott guidelines and if we ever needed to contact the participant by telephone, we would always check with the GP first to avoid troubling to ensure that the participant was alive and well. Although time to first recurrence might represent the most efficient method of utilising all of the data in terms of person-years, interpretation of such an outcome to daily practice may be difficult. Clinicians and patients are more likely to be guided by 3 or 5 year success rates.

In order to explore patient acceptability more thoroughly, we will ask participants for their views about treatment preference at the beginning of the study. At the end of the study, we will ask participants whether they would be keen to have the treatment option again (for both surgery and imiquimod).

Other baseline variables, which could influence treatment response, to be collected will include tumour thickness, tumour size, age, sex, number of BCCs at presentation, Fitzpatrick skin type, family history of skin cancer and an estimate of previous cumulative UV exposure.

Adverse Events will be collected from all participants up to the 1 year visit. After this time point, only those considered serious or related to the trial comparators (Imiquimod or Surgery) will be collected.

Definitions as to what constitutes an Adverse Event and an Adverse Reaction along with definitions of Seriousness and Severity and can be found in Section 3 of the Nurse Manual. This section also provides detailed instructions on the necessary reporting requirements.

3.6 Will health service research issues be addressed?

Yes – The economic evaluation of excision surgery versus imiquimod 5% cream for nodular and superficial basal cell carcinoma (BCC). The purpose of economic evaluation is to establish the change in resource use and the change in effectiveness brought about by the study intervention compared to comparative interventions. The cost-effectiveness of imiquimod as treatment for genital warts has already been demonstrated[49]. The cost-effectiveness analysis will compare the use of imiquimod 5% cream with excision surgery for nodular and superficial basal cell carcinoma (BCC).

In order to perform a full economic evaluation, cost data will be collected simultaneously alongside outcome data. These will include direct costs such as extra visits, travel, OTC medicines, health service resource use and indirect costs such as time-off work for a carer to accompany patients or related side effects.

Thus there will be two strands to this work, a costing study and an effectiveness study. In the effectiveness study, the primary outcome measure is clinical success rates. This is important and informative for decision makers. This will generate a probability of recurrence in both groups. Cost-effectiveness ratios will therefore

reflect the change in cost and change in probability of recurrence. This would be from a societal perspective since we are aiming to demonstrate the net economic impact of moving from one activity to another.

However, patient reported outcomes are also relevant, as this will inform us of other benefits and their relative value to these individuals. Measuring impact on quality of life for a tumour which causes little impact on quality of life in the first place may be futile. However, aesthetic appearance, pain, anxiety and stress should be captured in the economic analysis. The preferred method of doing this would be through conjoint analysis. This would entail adding some "willingness to pay" questions for certain hypothetical scenarios for participants (eg convenience of cream at home versus the "one-off" nature of surgery). We would gather such data in order to enable us to perform a cost-benefit analysis.

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 1997.). The study team will first identify all relevant resource consuming activities associated with both treatment strategies and for inclusion in the evaluation. Using a random sub-sample of participants at each centre in the trial, appropriate methods of measuring/quantifying this resource use will be developed. This will involve observing health service use (inputs of resource such as labour time, drugs, materials etc.) and patient (& their families) resource use. It is important to report this frequency of resource use as a result of the study as this will facilitate greater generalisability. Decision-makers in different settings with different cost structures can than apply their own unit cost data to the frequency of resource data produced in the study. To show the cost implications in this study resource frequencies will be valued by applying unit cost data from local sources (where available) and other available surveys (ref. Netten et al Unit cost of Community Care, PSSRU, University of Kent, 2000).

Thus the deliverables from an economic evaluation are as follows:

1. A cost-comparison analysis (net impact of all resource changes) of the two treatment strategies.
2. A cost-effectiveness analysis presented in the form cost per 'cleared participant'.
3. A valuation (in monetary terms using willingness to pay) of the perceived benefits of both treatment strategies, which (depending on results) could be incorporated into a cost-benefit analysis.

3.7 What is the proposed frequency/duration of follow-up?

Phone call at 2 weeks to discuss any early problems, followed by clinic follow-up by the dedicated research nurses at 6 weeks, 12 weeks, 18 weeks, 6 months and 1 and 2 years as shown on the synopsis flow chart. The dermatologist will also see the participant briefly, as part of the research nurse visit, at 12 weeks (surgery only), 18 weeks (superficial, imiquimod only), 6 months (nodular, imiquimod only), 1 and 2 years. The final clinical assessment of recurrence at 3 years will be done by the dermatologist, as would happen in normal practice. Such a long follow-up is essential since 82% of recurrences occur within this period[46]. We will also commit ourselves to a postal follow-up of documented recurrences at 5 years by writing to GPs, hospital clinics and obtaining pathology records.

A help-line will be available throughout the study to deal with participant/GP queries. There will be an opportunity for study participants to attend clinic so that any adverse reactions can be seen and recorded. Those participants who develop a brisk inflammatory response to imiquimod to the extent that they find it difficult to continue will be encouraged to have a one week "rest" period. This should allow the inflammatory reaction to settle in the same way as is currently done for such reactions with topical 5-fluorouracil. Treatment would then re-commence at a reduced frequency of five days a week for the total recommended treatment period, or for as long as the participant will tolerate. If the inflammatory response disappears completely the frequency will be increased again to seven days a week. If the response is again intolerable a week's rest and reduction to five days a week will again follow. There will be no further

attempt to increase the frequency. These participants will be analysed with the main data with an appropriate sensitivity analysis including and excluding them. Participant concordance with the cream will be recorded by asking participants to record use of the cream in a daily diary, and to return their used sachets (one per day of treatment) at the end of the treatment period. Any participants who develop a suspected recurrence (as judged by the participant's assessor or GP) will be referred back to the dermatologist/surgeon for a further opinion with regards to the need for further treatment, as happens in normal practice. This includes a "fast track" appointment system that sees patients with suspected recurrences within two weeks.

3.8 How will the outcome measure be measured at follow up?

Assessment of possible clinical recurrence of target tumour will be done in hospital by the dermatologist at the designated follow-up times. The main outcome measure of "success rate" at 3 years will also be assessed by the dermatologist. The target tumour site will be identified using digital photographs taken using a grid system prior to randomisation. Aesthetic appearance of target tumour following treatment is to be assessed by the participant in hospital with reference to original photograph, and also by a blinded outcome assessor using photographs. Participant pain diaries will be returned at the clinic visits or by post (pre-paid mail), as appropriate. Tolerability will be measured according to checklist administered during each telephone interview or visit.

3.9 What are the proposed practical arrangements for allocating participants to trial groups?

One lesion per patient will be chosen for the study, so that the unit of analysis will be patients rather than tumours. For those patients with multiple suitable BCCs (as identified and recorded by the investigator), the research nurse will pick one as follows out of those that the patient or doctor want entered into the trial (i.e. those that may be treated by either cream or surgery). The decision should be made *before* randomisation.

- The one that the patient is most bothered about, or first went to the doctor about
- If that does not apply, or the tumour in question does not meet the criteria, then the one that is easiest for the patient to reach.
- If this applies to more than one, the biggest will be chosen.
- If the patient wants both nodular and superficial BCCs treated, then a nodular BCC should be chosen to ensure there is enough cream for all (i.e. 12 weeks rather than six weeks of cream). If it happens that the histology shows the chosen nodular lesion not to be a BCC, but a superficial one is (assuming it had a biopsy), then the patient should be withdrawn, and re-randomised by the superficial BCC list.

Other current BCCs may be treated in the same way as the randomised one if the patient wishes, but this option should only be offered if needed, and BCCs are clinically suitable.

The identified BCC will then be biopsied. If the biopsy results indicate that the tumour is unsuitable for the trial, the patient will not recruited, unless there are biopsy results from other suitable lesions and the patient can be recruited without further delay. The remaining lesions will be treated as per standard practice (usually surgery).

Once suitable histological biopsy results are obtained, all patients eligible for inclusion and for whom consent has been obtained in this parallel group study will be randomised to topical imiquimod or surgery, according to a pre-prepared randomisation schedule, which has been generated by computer by colleagues at the Trent Research and Development Support Unit (TRDSU) (formerly known as Trent Institute for Health Services Research). The allocation will be obtained while the participant is attending their baseline visit, using a central telephone randomisation service run by independent staff at the TRDSU, who are experienced in doing this for NHS trials.

Randomisation will be stratified according to whether the lesion is nodular or superficial (defined clinically, except in the situation where the clinical diagnosis was not BCC, but the histological diagnosis was nBCC or SBCC, in which case randomisation will be by the histological diagnosis) and by centre (since centre could

be related to surgical operator skill or response bias of different assessors). This approach will ensure concealment of allocation, and minimise the differences in the most important predictor baseline variable. It is likely that the randomisation process will ensure that other baseline variables which may determine treatment response such as the proportion with multiple BCCs are evenly matched in such a large study. We have discussed and chosen not to use a minimisation approach to randomisation as it introduces unnecessary complexity. Our philosophy is to keep the randomisation process as simple as possible to ensure recruitment and less susceptibility to errors. There will be no attempt to equalise numbers of nodular and superficial BCCs randomised. The participant's general practitioner and consultant will be informed about the participant's involvement in the study.

* see Addendum 1 to protocol for Alternative Biopsy Procedure at some hospitals

Participants allocated to imiquimod who are deemed to suffer from a recurrence or early treatment failure will be offered excisional surgery, once biopsy results are obtained or after a period of watchful waiting.

3.10 What are the proposed methods for protecting against other sources of bias?

The allocation sequence will be concealed from participants, healthcare staff and investigators. This will minimise selection bias – the major flaw that has hampered most BCC trials to date[3]. Masking of the two very different interventions will not be possible for participants, and only partially possible for observers since surgery inevitably leaves a linear scar. This potential information bias is clearly a weakness of the study, but we cannot see a way around the problem if pragmatic outcomes are to be used. We will test for dermatologists' observer bias at the 3 year visit by asking an independent panel of 3 dermatologists to judge "clinical success" from the high quality digital photographs. This could not replace the main outcome measure of assessment by the participant's own dermatologist however since inspection of a photograph does not equate with close examination using different views and use of palpation of the skin and/or dermatoscopy, which a dermatologist would use in practice.

Analysis will be according to the intention-to-treat principle. This applies to primary and secondary outcomes including cosmesis. Those participants who leave the area will be visited by the research nurse where possible or by contact through their GP if this is not possible. Participants who die during the study period will be included in the ITT analysis according to their last assessment category carried forward. The trial and full protocol will be registered with the Cochrane Skin Group Ongoing Trials Register which is open to public scrutiny. We will also apply for a unique trial number identifier with the UK meta-register of trials. Consumers with BCC have already been and will continue to be involved in commenting on the study design and conduct.

3.11 What is the proposed sample size and what is the justification for the assumptions underlying the power calculations?

Rationale: Based on initial 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.

Our rationale for calculating sample size is based on a 90% success rate for imiquimod cream, with a lower 98% confidence boundary of 84%. This figure of 90% is generally considered the lowest percentage that fellow dermatologists would consider *changing their practice now*, if imiquimod was found to be easy to use and acceptable in terms of side effects. This is based on the belief that other commonly used treatment modalities such as curettage or cryotherapy have success rates approaching 90%[3].

As can be seen from the power table below, our total sample size estimate is for **740 participants**.

Success rate for surgery group	95%	96%	**97%**	98%
Success rate for imiquimod group	90%	90%	**90%**	90%
Lower limit for imiquimod group	84%	84%	**84%**	84%
Sample size per group	384	358	**333**	306
Total sample size	768	716	**666**	612
Total sample size allowing for 10% dropout	854	796	**740**	680

Assumptions: For a 1-tailed significance with (alpha)=1%, power (1-β) = 80%, a percentage 3 year success with surgery of 97% and success rate for imiquimod of 90%, a lower 98% confidence limit of 84%.

Success rates for surgery have varied between 95% to 98%. We have chosen 97% on the basis that 4mm excision margins will be performed (where tissue sparing permits) in accordance with the recent British Association of Dermatology BCC treatment guidelines, and that those conducting surgery are all trained dermatological or plastic surgeons.

This sample size estimate is a conservative one as it considers imiquimod as a direct competitor to surgery or other treatments, as opposed to being used in series ie cream first and then surgery if it fails.

In the latter scenario, local purchasers and some dermatologists would consider success rates of as low as 70 to 75% to be useful if cost-effectiveness, convenience and good cosmetic results can be achieved. If the success rate for surgery is 97%, and we envisage a lower success scenario for imiquimod of around 75% (for nodular and superficial BCCs combined), then a sample size of 740 will "buy" us a lower 98% confidence boundary of 67% around such an estimate – a useful level of precision for informing policy.

Another reason for maintaining a conservative estimate of sample size is to provide sufficient scope for the cost-effectiveness analysis since cost data such as willingness to pay is typically skewed. A sample size of around 700 will also permit an adequate number for the analysis of genetic markers of treatment response (see genetics addendum).

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 patients (still assuming 80% power and 1% one-sided statistical significance). Calculations indicated that the additional gain in power from 400 to 600 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). For example, for a pessimistic 70% overall success rate for imiquimod at 3 years, then the 98% lower confidence limit for a sample size of 400 was 59% and this rose to 60% for a sample size of 500. There was a gain of just a further 1% for a sample size of 600. Similar changes for the lower 98% confidence interval were noted for 75% success rates for imiquimod ie. assuming a success rate of 75% for imiquimod and 97% for surgery, then the lower 98% confidence interval for a sample size of 400, 500 and 600 would be 64.5, 65.6 and 66.4 respectively,

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. 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.

Why don't we do two separate trials?
Given that the preliminary data on imiquimod suggests that success rates are lower for nodular when compared with superficial tumours, it might appear desirable to perform two separate trials on these groups. However, preliminary data on clinical and histological data at Nottingham suggests that the correlation between what a clinician deems to be nodular/superficial and what a histopathologist decides is not good. Even the definition of nodular lesions by histopathologists is somewhat arbitrary and is one which is based on a combination of the shape of clusters of darkly staining basaloid nests within the dermis and absolute depth of abnormal cells. In real life therefore, clinicians are unlikely to make an *a priori* decision on what constitutes a nodular and superficial lesion, and even if they do, their clinical view may not accord with what is seen down a microscope ie they may be wrong. We therefore feel justified in sticking to an overall primary combined analysis of superficial and nodular BCCs. There will be ample opportunity within this project to do a smaller clinico-pathological study of correlation and reliability of clinical/histopathological diagnosis, and our histopathologist (Dr. Alan Stevens) has already identified a Specialist Registrar who is keen to do this as one of the study's spin-offs.

3.12 What is the planned recruitment rate?
At the Queens Medical Centre Skin Cancer Centre, around 1000 patients with BCC's are seen each year. For various reasons (other studies, severe time pressures on clinical staff running large screening for suspected skin cancer, patients who are unable to wait or who do not fit inclusion criteria), we estimate that 300 patients would realistically be available each year. In order to boost recruitment rates and in order to avoid the "trial fatigue" associated with a long recruitment, we propose including two District General Hospitals in the study (Solihull and Chesterfield). Their inclusion will also increase the degree to which the results may be applicable to a more typical District Hospital setting. These additional centres are expected to recruit 100 participants each year. Of 22 patients with BCC who were given the participant information sheet in a skin cancer clinic in Solihull during the first week of November, 20 showed an interest in participating if such a trial were to exist.

Thus, after an initial set up time of three months it seems feasible and realistic to attain target recruitment within 18 months. Although these estimates might seem conservative, previous experience at running two large NHS trials on common skin disorders has taught us to be cautious in such an estimation.

Due to being slower than expected, recruitment has been extended to additional centres (see addendum 2).

3.13 Are there likely to be any problems with compliance?
Surgery is performed in the hospital and does not usually present problems with patient compliance. Soreness and redness at the site of imiquimod cream application and the long duration of daily treatment are factors which could compromise compliance in the imiquimod group. The application of the cream will be explained in hospital. Cards for monitoring daily pain will be given to the participants as required, and returned every six weeks (either at a visit or by post). A telephone help-line will be available for answering day to day problems. The study is designed to be a simple pragmatic one, which will not attempt to coerce participants into unnaturally high states of compliance that would not be replicated in real life. Participants will be asked to return any unused imiquimod to the assessors at their follow-up visits.

3.14 What is the likely rate of loss to follow-up
Evidence from previous BCC trials suggests a 10% loss to follow-up.

3.15 How many centres will be involved?

Initially three centres: Queens Medical Centre University Hospital, and two District General Hospitals (Solihull and Chesterfield). Recruitment extended to further centres (see addendum 2).

3.16 What are the proposed types of analysis?
Analysis will be undertaken on a modified intention-to-treat basis. The principal analysis will be the comparison of the proportion of participants successfully treated (no treatment failure or recurrence of BCC) at 3 years as determined clinically, using modified Poisson regression. Secondary outcomes of clinical success at 1, 2 and 5 years will be analysed in the same way. Time to first recurrence will be compared between treatment groups using ordinal regression analysis. Details of all analyses are given in a comprehensive statistical analysis plan.
Analysis methods for the genetic markers are described separately in the genetic markers addendum.

3.17 What is the proposed frequency of analysis?
An independent Data and Safety Monitoring Committee comprising of a dermatologist (Dr. Nick Telfer, Manchester), clinical epidemiologist (Prof Carol Jagger, Leicester) and statistician (Dr. Stephen Walters, Sheffield) will review data with the trial statistician relating to severe skin reactions. Prespecified safety reviews will take place when the first 6 month data are available.

Stopping rules: Originally, the team had considered two stopping rules: an early rule to mitigate against unacceptably high early treatment failures (based on number of participants entered), and a second mid-study glimpse of the data using futility analysis using stochastic curtailment as a means of evaluating whether the study on course to obtain a conclusive answer. However, it quickly became clear that the second futility analysis would be futile because most of the events (ie clinical "success" at 3 years) would start to occur towards the end of the study. Even if a group sequential design is used[50], the same problem occurs because of the relatively short recruitment period in relation to follow-up period. Using earlier surrogate measures at the mid-study stage may be misleading without precise knowledge of the shape of the success curve and would complicate the study unnecessarily. The study will therefore operate to one clear early stopping rule.

The purpose of this *early stopping rule* is 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 is lower than 60% in the imiquimod group at the 6-month assessment then the data monitoring committee will consider recommending stopping the trial for participants with nodular BCC. In this context, "success" means those who fail to show adequate clinical response to the cream plus those who drop 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 has been chosen in favour of a 3-month point, as participants with nodular BCC will still be receiving cream until 12 weeks and ample time is needed for any treatment-induced inflammation/scaling to settle before assessing whether there is any remaining tumour clinically.

If indeed the study needed to be stopped for those participants with nodular tumours because of unacceptably low initial clearance rates, then continuation of the study for superficial BCCs would still be possible and desirable. This would however alter the nature of the study and more centres would probably need to be recruited in order to meet the target sample size given that nodular tumours are far more common. In such a scenario, we would return to the CRC for further discussion/advice as to whether the study should continue with superficial BCCs only. It is important that the interim analysis is based on numbers of participants rather than time points as insufficient numbers of events might occur within a pre-fixed time frame.

Based on the much higher success rates for superficial BCC in Phase II studies, we do not feel any early stopping rule is needed for these tumours.

3.18 Are there any planned subgroup analyses?
Sub group analysis for participants with nodular and superficial BCCs separately.
Sub group analysis for trunk and head lesions and those greater than 15mm diameter. A sensitivity analysis will be done including and excluding those with BCCs who are immunosuppressed (eg transplant patients).

3.19 Has any pilot study been carried out using this design?
The six pilot studies comparing different frequencies of application and duration of treatments for imiquimod versus vehicle have been described in section 2.1. We have previously used high quality photography in assessing clinical outcomes in our NHS study of acne treatments in the community.

4 Trial Management

4.1 What are the arrangements for day-to-day management of the trial?

The study will be managed by a steering committee, a trial management committee and an independent data monitoring committee. The role of the steering committee will be to steer the major design, analysis, interpretation and dissemination issues relating to the study. They will meet as often as is necessary, but every 6 months as a minimum.
The trial management committee's role is to meet once a month initially to sort out the logistic and practical problems associated with the study and to ensure that the recruitment rates are kept on target and that data quality is maintained.
The data monitoring committee will meet once a year and consider safety issues and make decisions on the fate of the study in the light of interim analyses.

Mara Ozolins will be in charge of the day to day running of the trial. Mara has just successfully managed and delivered the NHS clinical trial of acne which exceeded our target recruitment of 600 participants. The trial will be run according to the latest MRC guidelines on good clinical practice, and modified as required by the new EU directives highlighted by the Medicines Control Agency (MCA) in their recent briefing (see *What's new* at www.mca.gov.uk). We will take up the MCA's kind offer to perform a site inspection to place us in a position of readiness to comply with the EU directives for good clinical practice.

Overall responsibility of delivering the study will reside with Hywel Williams. Responsibilities for clinical decisions for individual participants will rest with their supervising dermatologist/plastic surgeons.

Trial indemnity will be the responsibility of the University of Nottingham. The research nurses and trial coordinator will all hold honorary contracts with each of the three Trusts. This is a requirement of Research Governance.

4.2 What will be the responsibilities of the applicants?

Dr Fiona Bath-Hextall, University of Nottingham.
Role: Contact applicant; study design and co-ordination of protocol development, help with study management, study write-up and dissemination. Member of the Trial Management Committee and Steering Committee
Expertise: Study manager for BASC (Blood Pressure in Acute Stroke Collaboration); centre recruitment for IMAGES; systematic reviews.

Professor Hywel Williams, Dermato-Epidemiology, University of Nottingham
Role: Principal investigator with overall responsibility for delivering the trial on time, staff organisation, financial management, guarantor for data quality, study write-up and dissemination policy.

Expertise: Epidemiology, systematic reviews, evidence-based dermatology and clinical trials. Co-ordinating editor of Cochrane Skin Group. Principal investigator of NHS acne trial which successfully recruited its target of 649 participants, reporting 2003. Director of the Trent Institute for Health Services Research (now called the Trent Research and Development Support Unit).

Dr William Perkins
Role: Steering Group member and study collaborator (recruitment and surgery).
Expertise: Consultant Dermatologist at Queen's Medical Centre, Nottingham. Trained dermatologic surgeon with a research interest in skin cancer management

Dr. Leslie Millard (until Nov 2005 – now retired)
Role: Steering Group member and study collaborator (recruitment and surgery)
Expertise: Consultant Dermatologist at QMC and trained dermatologic surgeon with a research interest in skin cancer management. Chair of Mid Trent Cancer Network.

Dr Jan Bong
Role: Systematic review, recruitment and study write-up.
Expertise: Specialist Dermatology Registrar (Dermatology Consultant since 2004) and co-author of BCC systematic review

Dr. Irshad Zaki
Role: Steering Group member and study collaborator (recruiting and surgery)
Expertise: Consultant Dermatologist at Solihull and dermatologic surgeon trained at QMC with an interest in skin cancer management

Dr. Graham Colver
Role: Steering Group member and study collaborator (recruiting and surgery)
Expertise: Consultant Dermatologist at Chesterfield with an interest in skin cancer management and postgraduate training.

Dr. Paul Miller
Role: Steering Group and dedicated health economist to study
Expertise: Health Economist affiliated to the TRDSU with expertise in clinical trial evaluations, working with Professor Dave Whynes.

Dr Sarah Armstrong
Role: Steering Group and study statistician
Expertise: Statistician at TRDSU with particular expertise in cancer epidemiology and clinical trials

Mr. Graeme Perks
Role: Steering group member, recruitment, surgery, and dissemination to plastic surgery colleagues.
Expertise: Consultant plastic surgeon working with the Nottingham multidisciplinary skin cancer team. Also lead for skin cancer research at the Nottingham Cancer Centre.

The trial will be based at the Centre of Evidence-Based Dermatology at Queens Medical Centre, Nottingham.

Members of the **data monitoring committee** include:

1. Dr. Nick Telfer (chair). Consultant dermatologist specialising in skin surgery at Hope Hospital, Manchester. Dr. Telfer is also lead author of the British Association of Dertmatology BCC treatment guidelines.
2. Dr. Stephen Walters. Medical statistician at the School of Health Related Research (ScHARR) at Sheffield and member of the Trent MREC committee.
3. Professor Carol Jagger, Epidemiologist at the Leicester Trent RDSU

4.3 What will be the responsibilities of the staff employed on the grant?
Mara Ozolins – trial manager as specified in section 4.1 (4 days a week initially, changing to 3 days a week from March 2004 post maternity leave). Accountable to Prof Williams with the following duties: managing steering group, design & creation of data capture forms (CRFs), design & arranging printing of diary cards, production of guidelines for assessors, training of assessors on collection of data, completion of forms & data entry onto lap-tops, on-site monitoring of standards, design and creation of database, resolving discrepancies in data recording and double data entry, general administration including: reports to ethics committees, arranging steering group meetings and writing minutes, stationery, freepost service for participant returns, coordination of pharmacy supplies and supervision of assessors. Data quality will be ensured by 3 monthly audits against original CRFs. Mara has been chosen for this position due to her experience and outstanding management of a major NHS HTA acne trial which is now coming to a close.

Three research nurses (0.4 whole time equivalent each; as of January 2004 the Nottingham-based nurse increased hours to 0.6fte in order to recruit from King's Mill Hospital). Main task is to recruit and follow-up participants and to enter data. They will be responsible to Mara Ozolins and will serve on the trial management committee.
Lab technician (to be appointed) for 1 year at Keele University – handling, preparation and analysis of blood samples for genetic testing.

4.4 What will be the roles of the named collaborators?
Prof Dick Strange, Dr. John Lear and Dr. Anthony Fryer – analysis of blood samples for possible genetic markers of BCC growth, which might predict treatment responsiveness. Please see genetic markers addendum for details.

4.5 Who is the trial statistician?
Dr. Sarah Armstrong, based at the Nottingham Unit of the TRDSU. Sarah has also received advice from Dr. Paul Silcocks, senior lecturer from the TRDSU.

4.6 Has ethics committee approval been obtained?
Full ethical committee and R&D director approval has been granted to the project for the main study site at Queen's Medical Centre. Ethical committee approval has also been granted for Chesterfield and Solihull. Ethical and R&D approval will be obtained for any new centres.

4.7 What measures have (will) you take to ensure that patients entered onto the trial are informed about its results.
We will write to each participant individually and to their GP with a summary of the study's main findings. We will engage consumers in writing such a leaflet. We will also run a lunchtime and evening session presenting the results to the study participants in order to allow them more direct feedback to the study team, as we have done with our NHS trials.

5. Financial details of the trial
5.1 Financial summary

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Staff costs						
Postdoctoral Research Fellow RA Grade II sp 110 (0.8 wte)	21338.3	22169.4	23036.6	23926.4	25269.0	115739.7
Three Research nurses Grade E (non-Uni) sp2 (0.5 wte)	34314 (11438 x 3)	34914 (11638 x3)	34914 (11638 x 3)			104142
Note: to be employed as Nurse grade F (Uni) 0.4 wte – total costs similar						
Recurrent expenditure						
Pharmacy dispensing	2000	2000				4000
Labels	700					700
Consultancy fees for statistician and health economist	1200				1200	2400
Extra dermatopathology costs			2500	2500		5000
IT Support	200	200	200	200	200	1000
Secretarial support	2000	1000	1000	1000	2000	7000
Equipment						
Digital Camera x3 (Sony Mavica MVC-SD87)	1400					1400
Lap top computer x3 (ACER 525 pentium 3 laptop)	3600					3600
PC desk (ITC Pentium 3 system)	1000					1000
Filing cabinets 6@80.00		240	240			480
Other costs						
Steering Meetings	200	200	200	200	200	1000
Consumables to include printing, stamps, discs	1500	500				2000
National and overseas meetings for results dissemination					2000	2000
Renting storage space for 10 yrs storage of clinical trial material					2000	2000
Feedback to participants					500	500
Travel for participants-additional 5 visits follow up (£20/participant)	2800	2800	2800	2800	2800	14000
Advertising for posts	1200					1200
Reprint requests for main article				400		400
Inter-library loans 20 papers @ 4.60	92					92
	73544.3	64023.4	64890.6	31026.4	36169	269653.7

5.2 Justification for support requested

Postdoctoral research fellow (0.8 wte) needed for the day-to-day management of the trial. The other day will be spent teaching/consulting at the TRDSU.

Three research nurses (one located at each centre to coincide with skin cancer clinics) needed to recruit, consent and follow up participants. Given that around 40 patients on average are seen in one 3 hour skin cancer screening clinic, it is quite unrealistic to expect the clinicians to have time to explain the study and consent participants. It is also our experience from a recent NHS eczema trial that it is essential to have a physical presence of a research nurses at collaborating centres if participants are to be recruited from those centres. Our experience to date with dermatologically-trained nurses has been a very positive one.

Three digital cameras needed for taking pictures of the BCC for location and to compare aesthetic appearance before and after treatment.
Three laptop computers (one for each centre) – data entry straight onto the database and storing of digital image of BCC.
Desk top computer – to be used by the postdoctoral research fellow for day to day running of trial.
Travel expenses for participants – participants will need to attend hospital for an additional 7 visits. Costs reflect cost of petrol and parking fees. Skimping on travel reimbursement will adversely affect recruitment.

Conflicts of Interest

None of the applicants have received any funds from the manufacturer of imiquimod cream (3M). All final decisions regarding trial design and data ownership reside with the study team and CRC. The chief investigator (Prof Williams) has never conducted any industry-sponsored trials and he does not work as a consultant for any drug company. He and members of his team have received funding for 3 major NHS trials from the NHS R&D Health Technology Assessment Programme. Prof Williams works as a paid consultant for the Consumers' Association (*Drugs and Therpeutics Bulletin).*

Acknowledgements

The applicants would like to thank the following people for their kind support and helpful comments in the development of this protocol:

Professor Robin Marks, Fitzroy, Australia
Mr. David Potter, Sittingbourne (Consumer with the Cochrane Skin Group)
Mr. Jack Tweed, Nottingham (Consumer with the Cochrane Skin Group)
Professor Jim Carmichael (CRC Oncology Professor, Nottingham City Hospital)
Professor Jack Hardcastle, R&D Lead for Cancer, Trent Cancer Network
Dr. Veronica Tebbs, 3M Healthcare Ltd.
Dr. Kim Thomas, Centre for Evidence-Based Dermatology
Dr. Huw Jones-Jenkins, Business Development Officer (and former MRC trials advisor). School of Medical and Surgical Sciences, University of Nottingham.
Trent Cancer Registry Information Service

References

1. Preston DS, Stern RS. Nonmelanoma cancers of the skin. N Engl J Med 1992; 327: 1649-1662.

2. Miller SJ. Biology of basal cell carcinoma (part1). J Am Acad Dermatol 1991; 24: 1-13.

3. Telfer NR, Colver GB, Bowers PW. Guidelines for the management of basal cell carcinoma. Br J Dermatol 1999;141:415-23.

4. Goodwin RG, Roberts, DL. Skin cancer registration in the United Kingdom. Br J Dermatol 2001;145(Suppl.59):17.

5. Wallberg P, Skog E. The increasing incidence of basal cell carcinoma. Br J Dermatol 1994;131:914-5

6. Holme SA, Malinovszky K, Roberts DL. Changing trends in non-melanoma skin cancer in South Wales, 1988-98. Br J Dermatol 2000 Dec;143(6):1224-9.

7. Chuang TY, Popescu A, Su WP, Chute CG. Basal cell carcinoma: a population-based incidence study in Rochester, Minnesota. *J Am Acad Dermatol* 1990;22:413-7.

8. Marks R, Staples M, Giles GG. Trends in non-melanocytic skin cancer treated in Australia: the second national survey. *Int J Cancer* 1993;53:585-90.

9. Gilbody JS, Aitken J, Green A. What causes basal cell carcinoma to be the commonest cancer?. Aust J Public Health 1994;18:218-21.

10. Zaynoun S, Ali LA, Shaib J. The relationship of sun exposure and solar elastosis to basal cell carcinoma. J Am Acad Dermatol 1985; 12: 522-525.

11. Pearl DK, Scott EL. The anatomical distribution of skin cancers. Int J Epidemiol 1986; 15: 502-506.

12. Mackie RM, Elwood JM, Hawk JLM. Links between exposure to ultraviolet radiation and skin cancer. A report of the Royal College of Physicians. J R Coll Physicians Lond 1987**;** 21: 91-96.

13. Leman JA, McHenry PM. Basal cell carcinoma. Still an enigma. *Arch Dermatol* 2001;137:1239-40

14. Hunter DJ, Colditz GA, Stampfer MJ, Rosner B, Willett WC, Speizer FE. Risk factors for basal cell carcinoma in a prospective scohort of women. *Ann Epidemiol* 1990;1:13-23.

15. Schreiber MM, Moon TE, Fox SH, Davidson J. The risk of developing subsequent nonmelanoma skin cancers. J Am Acad Dermatol 1990; 23: 1114-1118.

16. Booth DR. The hedgehog signalling pathway and its role in basal cell carcinoma. Cancer Metastasis Rev. 1999;18(2):261-84.

17. Bale AE, Yu KP. The hedgehog pathway and basal cell carcinomas. Hum Mol Genet. 2001 Apr;10(7):757-62.

18. Ramachandran S, Fryer AA, Smith AG, Lear JT, Bowers B, Hartland AJ, Whiteside JR, Jones PW, Strange RC. Basal cell carcinomas: association of allelic variants with a high-risk subgroup of patients with the multiple presentation phenotype. Pharmacogenetics 2001;11:247-54.

19. Roenigk RK, Ratz JL, Bailin PL, Wheeland RG. Trends in the presentation and treatment of basal cell carcinomas. J Dermatol Surg Oncol 1986;12:860-865.

20. McCormack CJ, Kelly JW, Dorevitch AP. Differences in age and body site distribution of the histological subtypes of basal cell carcinoma: a possible indicator of differing causes. Arch Dermatol 1997;133:593-596.

21. Breuninger H, Dietz K. Prediction of subclinical tumor infiltration in basal cell carcinoma. J Dermatol Surg Oncol 1991; 17: 574-578.

22. Gussack GS. Schlitt M. Lushington A. Woods KE. Invasive basal cell carcinoma of the temporal bone. *Ear, Nose, & Throat Journal. 68(8):605-6, 609-11*

23. Franchimont C. Episodic progression and regression of basal cell carcinomas. Br J Dermatol 1982; 106: 305-310.

24. Takenouchi T, Nomoto S, Ito M. Factors influencing the linear depth of invasion of primary basal cell carcinoma. Dermatol Surg. 2001 Apr;27(4):393-6.

25. Woolf DJ, Zitelli JA. Surgical margins for basal cell carcinoma. Arch Dermatol 1987;123:340-4.

26. Thissen MR, Neumann MH, Schouten LJ. A systematic review of treatment modalities for primary basal cell carcinoma. Arch Dermatol 1999;135:1255-9.

27. Wang I, Bendsoe N, Klinteberg CAF, et al Photodynamic therapy vs. cryosurgery of basal cell carcinomas: results of a phase II clinical trial Br J Dermatol 2001;144:832-840.

28. Williams HC. Dermatology. In: Stevens A, Raftery J. *Health Care Needs Assessment* Second series. Oxford, Radcliffe Medical Press, 1997, 261-348.

29. Eedy DJ. Non-melanoma skin cancer and the 'new National Health Service': implications for U.K. dermatology? Br J Dermatol 2000;142:397-400.

30. Testerman TL, Gerster JF, Imbertson LM, Reiter MJ, Miller RL, Gibson SJ et al. Cytokine induction by the immunomodulators imiquimod and S-27609. J Leukoc Biol 1995;58:365-72.

31. Slade HB, Owens ML, Tomai MA, Miller RL. Imiquimod 5% cream. Exp Opin Invest Drugs 1998;7:437-49.

32. Imbertson LM, Beaurline JM, Couture AM, Gibson SJ, Smith RM, Miller RL, et al. Cytokine induction in hairless mouse and rat skin after topical application of the immune response modifiers imiquimod and S-28463. J Invest Dermatol 1998;110:734-9

33. Beutner KR, Spruance SL, Hougham AJ, Fox TL, Owens ML, Douglas JM jn. Treatment of genital warts with an immune response modifier Imiquimod. J Acad Dermatol 1998; 38;230-9

34. Beutner KR, Tyring SK, Trofatter KR, Douglas JM Jn, Spruance SL, Owens ML et al. Imiquimod , a patient applied immune response modifier for treatment of external genital warts. Antimicrob Agents Chemother 1998;42:798-94

35. Edwards L, Ferenczy A, Eron L, Baker D, Owens ML, Fox TL, et al. Self-administered topical 5% imiquimod cream for external anogenital warts. Arch Dermatol 1998;134:25-30

36. Beutner KR, Geisse JK, Helman D, Fox TL, Ginkel A, Owens ML, Therapeutic response of basal cell carcinoma to the immune response modifier imiquimod 5% cream. J Am Acad Dermatol 1999;41:1002-7

37. Bavinck JN. Biological treatment of basal cell carcinoma. Arch Dermatol;136:(check page nos)

38. Marks R, Gebauer K, Shumak S, Amies M, Bryden J, Fox TL, Owens ML. Imiquimod 5% cream in the treatment of superficial basal cell carcinoma: results of a multicenter 6-week dose-response trial. J Am Acad Derm 2001;44:807-13.

39. Geisse JK, Marks R, Owens ML, Andres K, Ginkel AM. Imiquimod 5% cream for 12 weeks treating superficial BCC. Abstract P58 at 8th World Congress on Cancers of the Skin, Zurich, Switzerland 18th-21st July 2001.

40. Sterry W, Bichel J, Andres K, Ginkel AM. Imiquimod 5% cream for 6 weeks with occlusion treating superficial BCC.. Abstract P61 at 8th World Congress on Cancers of the Skin, Zurich, Switzerland 18th-21st July 2001.

41. Shumak S, Marks R, Amies M, Andres K, Ginkel AM. Imiquimod 5% cream for 6 weeks treating nodular BCC. Abstract P55 at 8th World Congress on Cancers of the Skin, Zurich, Switzerland 18th-21st July 2001.

42. Robinson JK, Marks R, Owens ML, Andres K, Ginkel AM. Imiquimod 5% cream for 12 weeks treating nodular BCC. Abstract P57 at 8th World Congress on Cancers of the Skin, Zurich, Switzerland 18th-21st July 2001.

43. Government HM. The New NHS. Modern. Dependable. London. The Stationery Office Ltd 1997; Clause 1.13:

44. Morris A, Emerson RM, Bong J. Skin cancer and the 2-week wait: is there a price to pay? Br J Dermatol 2001;145(Suppl.59):31.

45. McGovern TW, Leffell DJ. Mohs surgery. Arch Dermatol 1999;135:1255-59.

46. Rowe DE, Carroll RJ, Day CL Jr. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. J Dermatol Surg Oncol 1989;15:315-28.

47. Petit JY, Avril MF, Margulis A, Chassagne D, Gerbaulet A, Duvillard P, Auperin A, Rietjens M. Evaluation of cosmetic results of a randomized trial comparing surgery and radiotherapy in the treatment of basal cell carcinoma of the face. Plastic and Reconstructive Surgery 2000;105:2544-51.

48. Shum KW, Gawkrodger DJ. Low cure rates using currettage with cautery, and cryotherapy for basal cell carcinomas: audit of compliance with national guidelines. Br J Dermatol 2001; 145 (Suppl.59): 84.

49. Langley P et al. The cost-effectiveness of patient-applied versus provider-administered intervention strategies for the treatment of external genital warts. Am J Managed Care 1999;5:69-77.

50. Pocock SJ. When to stop a clinical trial. Br Med J 1992;305:235-40.