Re: 16-08236 - Chemoprevention of Basal and Squamous Cell Carcinoma with a Single Course of 5-Flourouracil 5% Cream: A Veterans Affairs Randomized Controlled Trial

This supplement contains the following items:

1. Original Protocol
2. Final Protocol
3. Summary of changes to the protocol
4. Original statistical analysis plan
5. Final statistical analysis plan
6. Summary of changes to the statistical analysis plan
1. Original Protocol V1.0
TABLE OF CONTENTS

EXECUTIVE SUMMARY ................................................................. 2
I.  BACKGROUND .................................................................................. 2
II. STUDY OBJECTIVES ....................................................................... 10
III. STUDY OUTCOME MEASURES ......................................................... 11
IV. PATIENT POPULATION ................................................................. 13
V.  INTERVENTIONS ............................................................................. 15
VI. ASSESSMENTS ................................................................................ 19
VII. ECONOMIC ANALYSIS ................................................................. 26
VIII. HUMAN SUBJECTS ....................................................................... 30
IX. QUALITY CONTROL PROCEDURES ................................................. 32
X. DATA MANAGEMENT AND DATA SECURITY ..................................... 34
XI. BIOSTATISTICAL CONSIDERATIONS ............................................. 37
XII. GOOD CLINICAL PRACTICES ...................................................... 43
XIII. STUDY ORGANIZATION AND ADMINISTRATION ......................... 48
XIV. PUBLICATIONS ............................................................................ 49
XV. REFERENCES .................................................................................. 51

APPENDIX A: DEFINITIONS FOR CENTRAL HISTOPATHOLOGY
APPENDIX B: DNA BANKING
APPENDIX C: CONSENT FORM
APPENDIX D: BUDGET
APPENDIX E: CURRICULA VITAE
APPENDIX F: BIOSTATISTICAL AND RESEARCH DATA PROCESSING
APPENDIX G: RESEARCH DATA FORMS (CASE REPORT FORMS)
APPENDIX H: DRUG TREATMENT AND HANDLING PROCEDURES
APPENDIX I: DRUG INFORMATION
APPENDIX J: TABLES

VA Central IRB approved version with changes. Approved on Nov 26, 2008.
EXECUTIVE SUMMARY

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin, both of which are keratinocyte carcinomas (KCs), account for a half of all cancers in the United States, and over 100,000 diagnoses per year in the VA. The standard treatment for these KCs is excision of the lesion, and they cost the US health care system some $2.5 billion annually and about $100 million annually in the VA. There is no proven means to prevent KCs (except perhaps for a modest benefit of intensive daily sunscreen use). An effective prevention strategy would dramatically change the way high-risk patients are managed and could substantially reduce the costs of care. Our preliminary analysis indicates that the savings will be $116 per high-risk patient and will account for a total national savings of over $11 million. These findings imply that the study would pay for itself by the end of 4 years. We hypothesize that topical 5-fluorouracil (5-FU) chemoprevention will prevent skin cancer surgeries and will be cost-saving. To test this we propose a randomized controlled trial of 5-FU compared to a vehicle control to the face and ears in a high-risk population.

In the study, 1000 veterans at high-risk of skin cancer defined as at least 2 KCs in the prior 5 years, at least one of which was on the face or ears, will be randomized to 5-FU or a vehicle control cream, and followed for 2 to 4 years. The primary endpoint will be surgery for any KC on the face and ears. We will also assess the cost of care, quality of life, the side effects associated with treatment, and the prevalence and number of actinic keratoses, a skin cancer precursor and itself a cause of morbidity and cost. By targeting patients at high-risk, the study focuses on high-cost patients for whom this treatment could both improve outcomes (cancers and quality of life) and reduce costs.

I. BACKGROUND

A. Abbreviations

KC: keratinocyte carcinoma (basal cell carcinoma and squamous cell carcinoma of the skin)

BCC: basal cell carcinoma, a type of KC

SCC: squamous cell carcinoma, a type of KC

AK: actinic keratosis, a precursor of SCC

5-FU: 5-fluorouracil, widely used as a 5% cream for topical application. It also comes in other forms.

NMSC: nonmelanoma skin cancer, which includes keratinocyte carcinomas, merkel cell carcinoma, cutaneous lymphoma, dermatofibrosarcoma, and a variety of uncommon cutaneous malignancies.
VAKCC Trial: The V. A. Keratinocyte Carcinoma Chemoprevention Trial, CSP #562, which is the subject of this proposal

VATTC Trial: The V. A. Topical Trentinoin Chemoprevention Trial, CSP #402, which is described in section 1.D

B. KCs and AKs

Each year, over a million cases of keratinocyte skin cancers are diagnosed, and about 40 million Americans have one or more AKs. The annual cost of KCs alone is about $2.5 billion\(^{12}\). In veterans, over 100,000 cases of KC are diagnosed each year, and the cost in the VA is estimated to be about $100 million annually.

BCCs and SCCs are keratinocyte carcinomas which share etiologic and clinical features\(^{1}\). Both malignancies arise in the epithelium, histologically resemble keratinocytes, and are caused in large part by exposure to ultraviolet radiation from the sun or artificial sources. Both are diagnosed by biopsy. Both are believed to result from a defect in DNA repair after ultraviolet light damage. Both occur at very high frequency and multiplicity in patients with Xeroderma Pigmentosum, a rare heritable disease characterized by more than a 1000-fold increase in BCCs and SCCs and by a defect in repair of ultraviolet-induced DNA damage\(^{47}\). These cancers are also more common with age and there is evidence that the DNA repair system in normal individuals becomes less efficient with aging.

While both BCC and SCC have sun exposure as their most important risk factor, they differ in other aspects. Iatrogenically immunosuppressed patients have very high risk of SCC, but not for BCC, and their SCCs are quite aggressive, whereas their BCCs are not\(^{21-23}\). PUVA (psoralen plus ultraviolet A) phototherapy results in increases in SCC that are well-documented and many times larger than the relatively modest, poorly documented association with BCC\(^{24,25}\). Even though BCC is about 3 times more common than SCC, SCC is responsible for more deaths because it is more likely to metastasize\(^{11}\).

BCCs and SCCs and the major precursor of SCC, actinic keratosis (AK), occur most commonly on the face and ears. About 60% of SCCs arise from AKs, and an estimated 0.025% of AKs progress to SCC each year\(^{2}\). Since a typical patient has many AKs, the risk of developing a SCC for the individual patient with AKs is about 1 to 2% per year\(^{3}\). There are no common clinical precursors of BCC. The treatment for both BCC and SCC is generally surgical.

The diagnosis of AK is generally made on clinical grounds alone, without a biopsy. However, histopathologic evaluation is done when there is concern that the lesion may be a KC. In population-based studies, the clinical impression is confirmed in over 90% of subsequent biopsies, but this figure is less than 90% in individuals with existing KCs\(^{4-6}\).

We propose to prevent surgeries for BCCs and SCCs by a cream applied to the face and ears, and thereby reduce the frequency of surgery for KCs on the face, and reduce morbidity from BCCs, SCCs, and precursor AKs. To determine its efficacy, we propose a randomized
trial of topical chemoprevention and its effect on skin cancer surgeries and cost, and occurrence of KCs and precursor lesions and quality of life.

1. KC is common and increasing in the US

KC is by far the most common cancer in the United States. Ten years ago an estimated one million cases were diagnosed per year in the United States. Since then the incidence has risen because of the aging of the population, the higher rates among the elderly, increased UV exposure from depletion of the ozone layer, and the rising popularity of indoor tanning in teenagers and young adults. Although the peak incidence of KCs is among the elderly, the long-term impact on younger adults permanently disfigured from facial KCs can be substantial. There has been a marked rise in the incidence of KC among young adults over the last 25 years, a 60% increase for BCC and over 300% increase for SCC. The rising incidence is likely to continue because more than three-quarters of one’s lifetime risk of KC is determined by exposures prior to the age of 18. Hence, potent preventive measures in this younger group, if adopted now, would not take effect until today’s young become old.

Veterans have a higher risk of KC now and in the future. Between 1999 and 2004, 777,768 KCs were diagnosed in 225,619 veterans. In FY03, there were 581,165 VA dermatology visits, of which 213,328 (37%) were for AKs. Veterans with service in areas of intense sun exposure, such as the South Pacific, Panama Canal Zone, Vietnam, Somalia, Lebanon, and the Persian Gulf have a greater risk of skin cancer.

2. KC causes significant morbidity and costs

Although KCs are usually cured, they cause considerable disfigurement and over a thousand deaths from KCs occur each year. KCs can cause local destruction of the nose, ear, and eyelid, producing deformity that leads to social isolation and rejection, facial paralysis (due to invasion of the facial nerve), visual impairment with loss of independence (when the orbit or eyelid is involved), breathing difficulties (from nasal deformity), hearing impairment compounded by inability to use conventional hearing aids (due to auricular deformity), chronic drooling (due to compromised function of the lip), ectropion and corneal erosions (from incomplete eyelid closure), and paraesthesias and sensory loss.

The economic analysis (Section VII) indicates that 5-FU treatment would save $116 per patient over 3 years. From 1999 to 2004 an average of 37,500 VA patients were diagnosed with a KC’s each year. At the end of three years, savings would accrue to $4,350,000.00 (37,500*116 = 4350000). To simplify, we round down to 4 million dollars as if we had saved $100 per patient for 40,000 patients. Then at the end of four years we will have saved a total of 11 million dollars: 4 million in year one, 4 million in year two, 2 million in year three, and 1 million in year four. After year two, we have discounted the subsequent cost benefit each year by 50%.
3. Prevalence and quality of life impact of AKs

AKs are estimated to cost Americans over $1 billion in direct and indirect costs. Of the 1131 veterans enrolled in the VATTTC Trial (CSP #402, see section 1.D), the number of AKs noted on their face and ears was a key correlate of worse quality of life on all three dimensions (i.e., symptoms, emotions, and functioning) independently of demographic factors or prior KCs.13

4. Diagnosis and Treatment of KC

BCC and SCC are diagnosed by examination and biopsy. The most common treatment for KC is surgical excision. When they occur on the face and ears, Mohs surgery is often used to conserve tissue and to completely remove the malignancy. The surgeon excises thin sections of tissue around the entire periphery of the tumor, meticulously maps the sections, and has each section systematically examined microscopically, thereby searching the entire border of the excised tumor tissue for evidence of malignancy. Wherever residual tumor is found, more tissue is removed and examined in the same manner. The process ends only when clear margins are achieved. Although more expensive and time-consuming than other surgical approaches, Mohs surgery has the highest cure rates among all modalities for treating KC’s on the face and ears, and is superior to all other surgical techniques in tissue conservation.

Surgical approaches used to remove KC’s at other body sites are seldom used on the face and ears because they tend to alter the appearance or damage tissue adjacent to the tumor and raise the risk of significant deformity. These alternatives include electrodessication and curettage. Cryotherapy with liquid nitrogen spray is also sometimes used, although the healing time is longer and the resulting scarring unsightly. All of these can generally be performed under local anesthesia, although this may not be adequate for the most invasive tumors or those requiring extensive reconstruction.

There are other treatments including radiation therapy and a treatment involving a topical application followed by blue light phototherapy that is known as “photodynamic therapy”. These other treatments are not commonly employed in most settings because of poor efficacy, lower efficiency, greater morbidity, or the requirement for specialized equipment.

Non-surgical therapies are not commonly used for KC’s on the face and ears. In particular, radiation therapy carries a risk of inducing additional malignancies over time. Thus, it may be used in elderly patients who cannot tolerate surgery.

Two topical chemotherapeutic agents have been approved for treating some types of KC: 5-FU and imiquimod. 5-FU is indicated for superficial BCCs when conventional methods are impractical, and imiquimod is approved to treat superficial BCCs in immunocompetent adults with tumors less than 2 cm on the trunk, neck, or extremities. Neither is commonly used for tumors on the face and ears because conventional surgery has higher cure rates.
5. Treatment of AK

AKs are usually treated by destroying the lesion with liquid nitrogen. Cryotherapy is an office procedure that produces pain during the procedure, typically followed by erythema and blister formation. The resultant erosion or ulcer may heal with permanent residual hypopigmentation. The other common treatment is topical 5-FU cream and the most typical regimen is 5% 5-FU cream bid for 2 to 4 weeks. This treatment may produce erythema, discomfort, and erosions which can be minimized by stopping therapy before significant erosions and crusting develop, even if the targeted duration has not been achieved. The clinical observation is that inflammation is most severe in areas of severe actinic damage and generally heals with no residual. Topical imiquimod is also used, typically 2-3 times per week for 16 weeks. It may result in the same side-effects, and the course of the inflammation is similar to 5-FU.

In the VA in FY03, 101,092 visits for AK had a CPT code of 17000 indicating destruction, by cryosurgery in the vast majority of cases. 96,067 had more than one lesion treated in that visit with destruction. In that same year, 32,740 patients in the VA received prescriptions for topical medications for AKs. Of these, 87% received 5-FU. The other medications included imiquimod (4266 patients) and diclofenac (110 patients).

The cost to the VA in 2007 is represented in the table below:

<table>
<thead>
<tr>
<th>Drug Name:</th>
<th>Cost of Drug</th>
<th>Cost per Application</th>
<th>Cost per Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% 5-FU</td>
<td>$80.42 / 40gm</td>
<td>$2.01(^1)</td>
<td>$160.84(^4)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>$56.10 / 50gm</td>
<td>$2.24(^2)</td>
<td>$280.50 – $448.80(^3)</td>
</tr>
<tr>
<td>Imiquimod (12 packets of 0.25mg)</td>
<td>$92.55 / 3gm</td>
<td>$30.85(^3)</td>
<td>$987.20(^6)</td>
</tr>
</tbody>
</table>

\(^1\) assumes a 1 gm application to cover face and ears  
\(^2\) assumes a 2 gm application based on package insert that indicates 0.5 gram covers 25 cm\(^2\)  
\(^3\) assumes 1 gm per application or 4 packets to cover face and ears  
\(^4\) represents the cost for two 40 gm tubes - assumes BID for 4 weeks  
\(^5\) assumes 2 gm application BID for 60 (5 tubes) to 90 days (8 tubes)  
\(^6\) assumes 1 gm treatment 2X week for 16 weeks

6. Chemoprevention studies of KC may provide insights into the process of carcinogenesis

KCIs are common, external and readily identified. Therapies may be externally delivered directly to large numbers of lesions or “pre-cancerous” regions. KCIs are a human in vivo model with transformative oncogenic pathways similar to other malignancies. For example, the RB, p53, RAS, and PTCH pathways all appear to play significant roles in the development of skin cancers \(^{15}\). Such pathway similarities have meaningful clinical
implications, such as the use of 5-FU for both colorectal cancer and cutaneous dysplastic lesions.\textsuperscript{16}

Prior studies of retinoids have demonstrated that findings in cutaneous chemoprevention trials can directly contribute to treatment applications for other malignancies. In 1988, retinoids were shown to provide effective chemoprophylaxis against the development of KCs in patients with xeroderma pigmentosum.\textsuperscript{17} These findings provided significant conceptual support for chemoprophylaxis studies involving lung, breast, hepatocellular, bladder, and cervical carcinomas. Furthermore, later studies of retinoids have shown that they may inhibit the progression of pre-malignant conditions and decrease the frequency of secondary malignancies in upper aero-digestive tract malignancies.\textsuperscript{18} This illustrates the value of KCs as models because they are easily monitored and sampled and quite common.

C. Prevention

1. Background

Despite much effort devoted to prevention of skin cancers the incidence continues to climb. Many governmental and nongovernmental organizations in the United States and elsewhere, notably Australia, have developed costly and sophisticated long-term public health campaigns aimed at the prevention of skin cancers.

The primary cause of KCs and AKs is ultraviolet light exposure. Hence it is commonly recommended to avoid sun exposure, use sunscreens, and wear sun protective clothing. The increasing incidence of skin cancers (BCC, SCC, and melanoma) over the past several decades suggest that this advice has been ineffective. Sunburn rates are not decreasing among U.S. youth or among Australians, and exposure to ultraviolet radiation is increasing as a result of the popularity of tanning salons (a risk factor for KC).\textsuperscript{20}

The advice to avoid sun exposure conflicts with advice for other diseases. Recommended physical activity to prevent cancer and cardiovascular disease involves outdoor activities. Many health outcomes depend on adequate levels of vitamin D, typically acquired by ultraviolet B exposure, which also increases KC risk.

There are no trials of sun avoidance or protective clothing use for the prevention of any type of KC or AK. High SPF sunscreen use has been demonstrated in randomized trials to be effective in reducing AK incidence and multiplicity,\textsuperscript{26,27} and one trial has suggested an effect in the reduction of SCC incidence, although no effect was found on BCC risk.\textsuperscript{28} BCC is about 3 times more common than SCC overall. In the VATTC trial (see I.D), participants were at high risk (similar to this proposed trial), and BCC was twice as common as SCC. As mentioned above, efforts at sun protection have not translated into a population effect of reduced BCC or SCC incidence, and is unlikely to do so in the near future.

Successful chemoprevention of KC results from systemic retinoids in high doses, but not from low doses.\textsuperscript{20,30} Retinoid compounds have significant side-effects, sometimes even at low doses,\textsuperscript{31} so they are not used for chemoprevention outside of quite uncommon settings.
that are associated with extraordinarily high risk such as xeroderma pigmentosum or solid organ transplant recipients on chronic immunosuppressive therapy\textsuperscript{32}. In an effort to avoid side-effects, we evaluated a high-dose topical retinoid for chemoprevention in the VATTTC trial (see section I D), and preliminary analysis suggested lack of efficacy.

2. Justification for chemoprevention treatment

There are no proven chemoprevention strategies for KC. Systemic retinoids are too toxic. It is common practice to treat actinic keratoses (AKs) to prevent SCC, but the efficacy of this practice, if any, is unknown.

Topical 5\% 5-FU was chosen for this trial because it has been in widespread use since 1972 and is the most widely used of the medical treatments for actinic keratoses. It has a long record on which to base assessment of safety. It is the only topical medication approved for use for facial BCC whereas other medications and other commercially available concentrations of 5-FU (2\%, 1\%, and 0.5\%) are not. It is less expensive than other medical treatments for AKs, including imiquimod, diclofenac, and photodynamic therapy.

5-FU is an analogue of uracil; the hydrogen at the C-5 position is replaced with fluorine. Intracellularly, 5-FU is converted into the active metabolites fluorodeoxyuridine monophosphate, fluorodeoxyuridine triphosphate and fluorouridine triphosphate. These active metabolites incorporate into RNA and DNA, as well as inhibit thymidylate synthase. 5-FU forms a stable complex with thymidylate synthase preventing the normal synthesis of dTMP necessary for DNA replication and repair. The downstream effects of thymidylate synthase inhibition and incorporation into RNA and DNA leading to inflammation and apoptosis are not well-understood\textsuperscript{33}.

It is common practice to treat AKs that are clinically apparent at the time of a visit to the dermatologist, whether or not they are symptomatic (bothersome) or have worrisome features. The most common treatment of AKs is cryotherapy (see I.C.2), which treats only one lesion, and does not have any effect on the remainder of the area (field) of skin. The second most common treatment in the VA is topical 5-fluourouracil cream (5-FU) applied to an area, not just to a particular lesion. The clinical impression is that when 5-FU is used to a field of sun-damaged skin, subclinical AKs become inflamed and resolve, as do the original, clinically recognized AKs.

Topical 5\% 5-FU is also approved for treating superficial BCC, but lower concentrations are not. 5-FU is not commonly used for BCC treatment because it does not have as high a cure rate as surgical excision or electrodessication and curettage.

Only one trial has compared 5-FU and imiquimod; it found 5-FU superior to imiquimod for the treatment of AKs\textsuperscript{34} but we judged that trial to be of poor quality, and noted that it was sponsored by a manufacturer of 5-FU. A systematic review was published of therapy for AKs\textsuperscript{35}, but the quality of the source studies (as well as the review itself) was so poor and the heterogeneity so great, including pooling of 1\% and 5\% 5-FU treatments, that reasonable
conclusions cannot be reached. We note that the first author is an advisor and trialist for the manufacturer of imiquimod.

Imiquimod is approved for treatment of certain types of BCCs, but not for use on the face, unlike 5-FU. It is more expensive, less commonly used, and it comes in a form for which a vehicle control cream with similar appearance would be difficult to formulate. Diclofenac is generally thought to be less effective for AKs and is not commonly used. Photodynamic therapy is complex, requires considerable staff time and patient time to perform, and methods for its use vary (often requiring long incubation times and residual photosensitivity). It also requires specialized equipment which is only available at a few VAMCs.

AKs are common precursors of SCC, but only a small proportion of AKs progress (see I.B.3). As noted above, AKs are commonly treated (usually by liquid nitrogen cryotherapy, a rapid, outpatient procedure that affects only the AK) because of this risk of progression; although it is not known whether and to what degree such treatment is effective in reducing SCC risk (see I.C.2). Unlike cryotherapy of AKs, topical 5-FU can be used on the entire face and ears, and has the potential to eliminate precursors that are not clinically apparent as well as visible AKs. We hypothesize this will result in the most effective prevention of SCCs.

There is no clinically recognized precursor of BCC, although subclinical keratinocyte dysplasias may give rise to BCC. Topical 5-FU is particularly worth evaluating because it is effective in the treatment of superficial forms of BCC, and is approved for that indication. It may also effectively treat clinically unrecognized BCC precursors. It should be noted that topical 5-FU is not commonly used to treat clinically evident BCC despite FDA approval for that purpose, because it is not as effective as complete surgical excision, nor is the healing after treatment of fully evolved lesions as rapid as with surgery.

3. Impact on Prevention

If successful, this treatment could markedly reduce KC in the VA population. As the cost analysis details, the short-term reductions would precipitate larger reductions in long-term direct costs and future morbidity because unlike other chronic diseases such as diabetes, KC does not shorten life. It is unlikely that any institution outside the VA would conduct a clinical trial to establish that this relatively inexpensive treatment, available in generic form, leads to less surgery and fewer costly treatments. Prevention of recurrences can result in major cuts in the expense of treating this disease.

D. The VATTC Trial (Cooperative Studies Program Trial # 402)

The VA Topical Tretinoin Chemoprevention (VATTC) Trial (study chairman Martin A. Weinstock, MD, PhD) was a randomized trial of a retinoid cream, tretinoin 0.1% vs. the vehicle control cream, applied to the face and ears up to twice daily, to test the hypothesis that the tretinoin would reduce the incidence of BCC and SCC. 76% of participants had AKs on the face and ears, and 37% had more than 5 lesions on the face and ears. Our
analyses indicate that the intervention was not effective. The trial met or exceeded recruitment goals, the intervention was delivered appropriately, and follow-up was 97%. The trial demonstrated that intervention was ineffective because the chemoprevention agent itself does not reduce BCC or SCC incidence.

It should be noted that in the VATTC Trial, the preliminary evidence supporting the use of this agent was based primarily on oral administration of retinoid compounds, which is, however, impractical for large scale chemoprevention because of the of the side-effect profile (hence the trial of the high-dose topical agent). For the proposed VAKCC Trial, however, the preliminary evidence reviewed above is primarily based on use of the topical agent itself. Hence we can be more confident of the likelihood of successful chemoprevention.

The VATTC study demonstrates the feasibility of recruiting sufficient subjects for the current proposal. A total of 1131 veterans from six clinical centers completed the study and were followed for up to six years. All centers but one recruited enough patients (that site had a coordinator who fell ill, worked in her impaired state for some time, and ultimately succumbed to her illness). At one study site protocol violations in an unrelated study forced the site to halt all research studies. Poor performance led the VATTC study to drop one site. The replacement site then recruited over 200 patients who completed the study, exceeding study goals.

The VATTC study obtained 6341 biopsy specimens from 913 of the 1131 patients randomized. 3919 (99.8%) of the face/ears biopsy specimens were read by central dermatopathology as well as the local pathologist. 34 (3%) of participants withdrew.

II. STUDY OBJECTIVES

Primary Objectives:

To determine the effect of topical 5-FU treatment (compared to a vehicle control treatment) on reducing surgeries for KC on the face and ears. This is to be determined in high-risk patients in a 4 year trial (2 years recruitment; average follow-up 3 years). Everyone in the trial will receive enhanced patient education and free sunscreen for the duration of the trial.

Secondary Objectives:

To evaluate the cost-effectiveness of this intervention, and effect of the 5-FU treatment on the incidence of surgery for BCC, on the incidence of surgery for SCC, on cryotherapy to the face and ears and prevalence of AKs, on quality of life, and on the frequency and severity of specific side-effects of the treatment.
III. STUDY OUTCOME MEASURES

A. Primary Outcome

The primary outcome will be the time to diagnosis of the first KC on the face or ears for which surgery is performed. By requiring surgical treatment, we are focusing on the more consequential lesions associated with morbidity and cost for our primary outcome. It should be noted, however, that we expect approximately 91% of the KCs diagnosed in this study to be treated surgically (based on our VATTC Trial experience), as this is the standard treatment. This outcome uses a time-to-event survival analysis comparing the hazard rates with the two treatments. We considered other approaches including use of total number of events, but the time-to-event approach offers statistical advantages, and it makes maximal use of the follow-up experience, hence shortening the overall study time by allowing the last patients enrolled to have a shorter follow-up period than the first patients enrolled.

Since we are evaluating chemoprevention, the primary outcome is surgery for primary lesions, not recurrent lesions. Recurrent lesions are recognized by their occurrence in the scar from prior removal of the cancer. We understand that recurrent lesions occur when malignant cells remain after removal or destruction of a KC, and those cells are frequently deep in the skin and therefore less suitable for treatment with topically applied agents.

This endpoint will be ascertained either at the scheduled follow-up study examinations or at examinations requested by the patient. At each study visit, the participant will be questioned about any skin cancers or surgeries that may have occurred since their last visit. Potential KCs will be managed according to the standard of care. Any potential KCs designated for surgical intervention will be noted for later tracking on Form22: KC Treatment, and the VA electronic record will be reviewed to ascertain or confirm the occurrence of the KC and the surgical procedure. For all participants in the trial, all local pathology reports of biopsies from the skin of the face or ears will be read and diagnosed at the clinical site. Corresponding pathology reports will be reviewed at the chairman’s office over the course of the study to confirm the diagnosis of all lesions biopsied or otherwise surgically removed. The histopathologic specimens of surgically removed lesions will be reviewed independently by the central dermatopathologists for the purpose of this study (see III.1). If a surgically excised lesion has the diagnosis of KC on initial biopsy, subsequent re-excision or Mohs surgery layers slides will not be sent for central review, since the lesion already has a centrally reviewed diagnosis of KC and hence qualifies as an endpoint. Skin cancers diagnosed outside of the VA, and associated surgeries, will be systematically sought in all participants to insure our outcome measure is complete. For any outside diagnosis or surgery, the medical record will be sought and reviewed. In the VATTC trial, 91% of KCs biopsied had a subsequent surgical treatment (some variety of excision or electrodessication and curettage), and diagnosis of KCs on the face and ears outside of the VA system represented only 1% of the total number of KCs on the face and ears during that 6-year trial.
We will use actual cancer occurrence for which surgery is performed, as opposed to occurrence of a precursor or intermediate marker, as the primary outcome because of the problems in the in reliability of diagnosis and counting precursor lesions\textsuperscript{36}, their variable natural history, which includes a high probability of apparently spontaneous resolution, and a small probability of progression to invasive cancer\textsuperscript{2,5}.

B. Secondary Outcomes

1. **Cost-effectiveness of the treatment strategy:** It is common for susceptible individuals to have multiple AKs and KCs. The cumulative resources devoted to their care and specifically the treatment costs are large (see I.B). The cost analysis will therefore look at potential short-term and long-term savings from this strategy in high-risk populations (see VII). KC treatments other than surgery, which are expected to be few, will also be included in this assessment.

2. **Time to occurrence of first BCC for which surgery is performed, and separately of first SCC for which surgery is performed:** The etiologic differences between BCC and SCC indicate that a chemopreventive intervention may have differential effects between the two histopathologic types of KC. As reviewed in Section I, there is substantial evidence that the proposed intervention will be effective for both histologic types. Since there are identifiable populations at greater risk for BCC, and others for SCC, delineating the value for each separately is worthwhile. We will also examine predictors of BCC and SCC occurrence.

3. **Number of BCCs, SCCs, and overall KCs requiring surgery per person-year of follow-up:** Because patients often will have multiple KCs, we will evaluate the number of BCCs, SCCs, and KCs per person-year of follow-up. This may show that the treatment reduces the overall numbers of KC over time.

4. **Time to occurrence of first KC, BCC, and SCC for which surgery is not performed.** This will allow us to determine any effect of the study intervention on a later decision to treat a skin cancer surgically, instead of by an alternative modality. The numbers not treated surgically are expected to be small (about 9% of KCs diagnosed), so only an (unexpected) large effect could be noted in this analysis.

5. **Measures of AKs:** We will also measure AKs because the morbidity and cost associated with these skin lesions is large (see section I). Also, the intervention tested has known efficacy against AKs, so reduced AKs and reduced need for treatment of AKs may be important benefits of the regimen. We will count AKs greater than 5 mm in diameter, a reliable measure\textsuperscript{37}. We will also count and measure cryotherapeutic treatments as an outcome; this is the standard treatment for AKs. Cryotherapy treatments will be a component of the cost-effectiveness analysis. Any treatments for AKs other than cryotherapy will also be measured.
6. **Surgeries not for KC:** We will examine whether there is a difference between groups in surgery on the face and ears for lesions other than KC. This will also be a component of the overall cost-effectiveness analysis.

7. **Side-effects of treatment:** Specific indices of chemopreventive treatment side-effects (especially pain, itch, sores/crusts, and erythema) will be ascertained. The measurement will include questions regarding the presence and degree of symptoms such as pain/burning and pruritus of the face and ears as well as erythema.

8. **Quality of life:** Skin cancer can cause substantial anxiety, disfigurement, and other morbidity. For quality of life, we will use the Skindex (a published, validated, widely used quality of life instrument for skin disease)\(^{38}\). This is a brief questionnaire completed by the participant. We will also use the Skin Cancer Index (a published, validated quality of life instrument for patients with nonmelanoma skin cancer).\(^{50-51}\)

Morbidity from KC may include both morbidity from the cancer and from the treatments. When cancer is diagnosed, treatment of AKs may result in short-term pain and long-term depigmentation that may be disfiguring. Hence the quality of life measures reflects morbidity due to the skin cancers, morbidity due to AKs, morbidity due to their treatment, and morbidity due to the chemoprevention interventions themselves.

9. **Exploratory analysis of endpoint location:** We will review photographs of endpoint lesions to ascertain any particular sub-areas on the face and ears at which the chemopreventive treatment may have been more or less effective.

10. **Nonsteroidal anti-inflammatory medications (NSAIDs):** We will assess use of NSAIDs (OTC and prescribed) to evaluate their relation to KC risk, since that association has been suggested but is controversial \(^{45,46}\).

**IV. PATIENT POPULATION**

The study population will be selected for being at high risk for BCC and SCC. Each site will develop their own recruitment strategy consistent with VA policy. All participants will have a skin examination by a dermatologist and be found free of skin cancer at the time of randomization.

**Inclusion Criteria:** Two or more KCs in the prior 5 years and at least one of those occurred on the face or ears. The KCs do not count toward the inclusion criteria if they occur in an area of radiation therapy or on genital or perianal skin. Among the 1131 randomized in the VATTIC Trial (see I.D), 976 (86%) had at least one facial/ear KC (that is by far the most common site for KC, see I.B.8), and therefore would meet these inclusion criteria. Among those 976, 47% developed at least one BCC endpoint (5-year life table probability 56%), and 25% developed at least one SCC endpoint (5-year life table probability 29%). The 5-
year probability of at least one KC was 69%. Insisting on a history of at least 1 KC on the face or ears will also mean that the patients are more likely to appreciate the rationale for chemoprevention, and will have increased motivation to comply with the treatment.

Exclusion Criteria:
1. Participants with KC at randomization.
2. Participants currently using or having used field therapy for AKs on the face or ears in the past 3 years. The vast majority of these field treatments would have been with 5-FU cream. We will allow recent use of therapies that are applied to individual AK lesions (e.g. cryotherapy), but not those that were used on an entire area (field) in the study treatment area.
3. Participants currently using or having used systemic 5-fluorouracil or oral capicitabine (Xeloda®) within the past 3 years.
4. Participants with known allergy to sunscreen, triamcinolone and/or 5-fluorouracil.

(Exclusions 5-10: We will exclude the small proportion who get their KCs for special reasons other than ultraviolet radiation exposure (see list below), since that etiologic difference, which is associated with a prognostic difference, could be associated with a biologic difference in response to chemoprevention efforts. These will include:

5. Solid organ transplant recipients, such as renal, hepatic, or cardiac transplant patients.
6. Individuals with genetic disorders associated with very high cancer risk such as
   A. basal cell nevus syndrome
   B. erythrodysplasia verruciformis
   C. xeroderma pigmentosum
7. Arsenic exposure
8. PUVA (Psoralen plus UVA) treatment
9. Cutaneous T-cell lymphoma
10. Prior or current radiation therapy to the face and/or ears

Additional exclusions (11-14) are:
11. Those who, in the opinion of the recruiting investigator, have very high mortality risk at randomization (less than 50% chance of surviving 4 years) due to comorbid illness such as metastatic cancer or COPD.
12. For women of childbearing potential an initial pregnancy test and ongoing birth control will be required for participation.
13. Patients with known dihydropyrimidine dehydrogenase (DPD) enzyme deficiency by self report or noted in the medical record (they have increased toxicity from systemic 5-FU, although screening for this is not part of dermatologic practice and will not be part of this study)
14. Patients on methotrexate (these will constitute about 1% of potentially eligible individuals) because they may have more severe reactions to topical 5-FU

Protocol v 1.0 9/29/08 Page 14 of 55
15. Non-english speaking individuals will be excluded from participation due to lack of translation resources at most local VA Medical Centers. All study questionnaires are currently written in English and the cost to translate these materials would be too high.

V. INTERVENTIONS

A. Stratification and randomization

The participating center will submit the screening and baseline data electronically to the Project Manager at CSPCC for immediate confirmation of qualification and randomization. Randomization lists will be generated at the CSPCC based upon permuted random blocks of variable size to assure approximate balance over time and will be stratified by study site. Allocation will be approximately equal between groups. The MS InfoPath/SharePoint electronic data capture system that is being developed will allow the entire process to be completed during one patient visit. The treatment assignment and kit number will be assigned electronically using these two systems and will then be sent to the VA Pharmacy Coordinating Center in Albuquerque. Staff in Albuquerque will track the assignments and ensure that all centers are properly supplied with study drug.

The study chairman’s office at the Providence VAMC will liaison with the other centers and assume primary leadership responsibility for the trial. The Boston VA Cooperative Studies Program Coordinating Center (MAVERIC CSPCC) will manage randomization and serve as the primary statistical and data management coordinating center for the trial. The Albuquerque VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) will manage drug supply, accountability, and review of adverse event and serious adverse event data. Eligibility criteria will be gathered, confirmed, and stored in a central electronic file. Drug assignments based on randomization will be entered in the same file. Assignments of treatment will then be made via the internet for all sites.

B. Interventions

1. **Both groups:**

All participants will receive detailed patient education about skin cancer, including images of typical early skin cancer lesions, and will be counseled on sun protection and the use of sunscreen. Sunscreen will be provided to the participants free of cost for the duration of the trial. All participants will also be given detailed instructions on how to apply the medication, and shown photographs of patients with moderate to severe reactions to 5-FU to illustrate a possible reaction to the study medication. Participants will be counseled on when they should discontinue use of the study medication and contact the study nurse. Patients will not be paid for joining this study, but will receive $20.00 to $40.00 per study visit to help cover the cost of gas and other travel expenses.

2. **Intervention group:**
The intervention group will have topical 5-FU 5% cream applied twice daily for 4 weeks to the face and ears, to be initiated immediately after randomization. The FDA-approved treatment for AKs is twice daily for 2-4 weeks (28 to 56 total doses), and for superficial BCC is 3-6 weeks twice daily (42 to 84 total doses). These two schedules overlap; for this study the treatment duration will be 4 weeks (56 doses). The 5-FU will only be given once although multiple treatments might potentially be more effective. We expect to be able to detect effectiveness of a single treatment. There are currently no data on which to determine the optimal interval between 5-FU chemopreventive treatments.

We hypothesize that the 5-FU treatment will destroy KC precursors, and because of their slow progression will therefore have a prolonged effect on KC incidence, despite the short course of treatment. The ultimate use of this chemopreventive strategy will undoubtedly involve re-treatment. The data from this study will guide estimation of duration of effect of a single treatment and the appropriate length of a re-treatment interval (see XI.G.1.).

If the participant is unable to tolerate the twice daily 5-FU, they will discontinue the treatment and initiate “cool-down” treatment with triamcinolone 0.1% cream twice daily until the symptoms resolve. In these reactions, symptoms generally resolve within the first 3 days. Asymptomatic erythema typically resolves in about 2 weeks. At 3 weeks after stopping 5-FU, if and only if the participant has not received at least the minimum 2 week (28 dose) course, 5-FU treatment will be resumed on a once-daily basis to complete the 56 dose course. If this is not tolerated, the “cool-down” routine will be followed, but 5-FU will be stopped. It is commonly assumed that the inflammatory response indicates an adequate dose of the topical 5-FU has been received, in which case even those who stop early are likely to benefit from the chemopreventive effect of the experimental cream. Adverse reactions to the study medications and use of triamcinilone will be tracked by the study nurse and recorded on the form 23.

Clinical experience indicates the importance of counseling regarding possible reactions for the successful use of this agent. This counseling will be provided by the on site study nurse, who will talk with all participants at each visit and bi-weekly by phone during the treatment. Study nurses will be trained for counseling prior to use and during use, and for appropriate handling of potential issues that may arise during and after treatment. Patients will be encouraged to call the study nurse with any questions that may arise during the study (see VB4). An additional unblinded dermatologist will be also be available to the participant at any time.

The placebo cream is a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl). The Efudex cream is 5% 5-Flourouracil in a vanishing cream base consisting of the same ingredients as the placebo. Based on these ingredients we do not expect study related adverse events due to use of the placebo cream other than the possibility of contact allergy or irritation.

3. Justification for focus on just face and ears:
There are four reasons for applying the chemoprevention treatment to just the face and ears in this trial. First, the face and ears represent just 3% of the body surface area, but 75% of KCs arise on these areas, so treating these areas is a cost-effective approach. In the VATTC Trial, which did not select for veterans with prior face/ear KCs (see section I D), 3449 (68%) of the 5080 KCs among participants during the 5 years prior to enrollment and 65% of the KCs that occurred during the trial were on the face and ears.

Second, KCs of the face and ears are the most consequential in terms of potential for visible or functional deformity and for impairment of vital structures such as the eyes, ears, nose, facial nerve, and skull (see Section I A). The ear in particular gives rise to up to 47% of the ultimately fatal non-genital SCCs.

Third, the limited surface area of application is likely to enhance compliance. When 5-FU is applied for AKs, it is usually done by the patient to the face and/or ears which gives us confidence in its use for the chemopreventive purpose in a population that has already had multiple skin cancers. In the VATTC Trial, the chemopreventive agent also caused dermatitis and was applied to the face and ears once or twice daily, but in that trial it was applied for up to 6 years.

Lastly, our treatment strategy (see I.C.4) is most likely to be effective in these areas, since these are the areas in which 5-FU is most effective in treating AKs. When 5-FU is used in other areas, longer courses of treatment are needed to see an effect. Based on this experience, one presumes that it is also more effective for clinically inapparent incipient KCs on the face and ears than for similar lesions elsewhere on the skin. If that presumption is correct, it is another reason that testing the chemopreventive potential of this treatment strategy would be more powerful if tested on the face and ears than if tested elsewhere on the skin.

4. **Blinding:**

The control group will receive a physically identical cream that does not contain the 5-FU.

The trial is triple blinded. The study dermatologist and dermatopathologists will be blinded to treatment assignment, and will determine the primary endpoint of the trial. The endpoints will occur long after the 5-FU treatment is completed, and any resulting reaction has subsided. In the absence of any topical applications to the skin, skin cancers may or may not be accompanied by histopathologic signs of inflammation.

Neither the patient nor the blinded study dermatologist will be informed of the treatment group assignment. The blinded study dermatologist will not evaluate the participants between randomization and the first 6 month visit, in order to maintain the blind (see below). The side-effects of the cream will result in some unblinding of the patient that is substantial but not complete. In the VATTC Trial, which involved daily or twice daily application of tretinoin 0.1%, a cream which also frequently produces skin inflammation, we observed that the placebo control group frequently noted symptoms of inflammation on the skin. Although considerable inflammation may be expected in many but not all individuals.
in this proposed VAKCC trial, we expect there will be overlap in this symptomatology between the experimental and control groups.

To ensure adequate assessment, treatment and reporting of adverse events, up to four clinical staff may be associated with this trial at each local site: a primary investigator who will be blinded to which treatment the subject is receiving; a secondary investigator who will also be blinded to treatment and will be available to see patients when the primary investigator is unavailable for study visits; a third dermatologist or dermatology nurse practitioner unblinded to treatment will be available during the treatment phase to clinically monitor the subjects, assess adverse events, and prescribe treatment for adverse events if necessary; and the study nurse.

Furthermore, all visits during the treatment phase will be with the study nurse, who may therefore become unblinded but who is not responsible for any of the study assessments that determine the primary outcome. Those are the responsibility of the study dermatologist, who will see the participant at randomization and at every six month visit, and the study dermatopathologists. The first 6 month visit will be long after any treatment-associated dermatitis or erythema has resolved. The participants will be instructed not to inform the study dermatologist about any reaction they may have had, and the study nurse will not inform the study dermatologist.

To assess the extent of unblinding, at the first regular (6 month) visit we will ask participants and dermatologists to guess whether they had received active treatment or placebo. Provisions will be made for unblinding if ever clinically required for the participants medical care, although this is unlikely.

5. Treatment of clinically diagnosed AKs:

Both groups will have cryotherapy treatments to individual spots on their skin as needed for clinically diagnosed AKs, as is the accepted standard clinical practice. "Spot" treatment to individual actinic keratoses with liquid nitrogen is by far the most common treatment of these lesions in the VA and nationwide (see I.C.2). It is not standard practice to biopsy AKs prior to treatment, and we will not require that here.

The key distinction here is between "spot" treatments, which will be allowed because they treat only the lesion and not an entire area of clinically nonlesional skin, and "field" treatments, which do treat an entire area, and will not be allowed (other than the experimental intervention). Spot treatments other than cryosurgery include curettage, electrodessication, or other surgical modalities, although these are not commonly used. A common feature of these spot treatments is that they are applied or performed by the clinician to the lesion only. Participants in both treatment groups will be allowed to receive these "spot" treatments as indicated, but will not be allowed to receive any of the "field" treatments unless the treating dermatologist concludes that other possible alternatives are unacceptable for this patient on medical grounds. Such instances will be quite rare, if they occur at all, and they will be recorded and reported to the study chairman's office. Similarly, participants in both treatment groups will not receive any of the "field" treatments.
during the course of this study other than the experimental treatment immediately after randomization. Examples of other “field” treatments include diclofenac and photodynamic therapy with aminolevulinic acid and blue light, as well as 5-FU not in the usual 5% strength (e.g. 2%, 1%, and 0.5%). Unlike the other field treatments, photodynamic therapy must be applied by a clinician, and can be used with the medication applied only to the lesion, or to an entire area. The former would be a form of spot treatment, the latter a form of field treatment.

VI. ASSESSMENTS

Patients will be assessed at baseline, at follow-up visits, and by telephone. We will also gather information from their medical records, and will conduct independent blinded central review of all biopsy specimens as part of this research trial.

Note that after randomization patients will return at six-month intervals for scheduled follow-up evaluations. They also may have unscheduled evaluations because of a lesion they have found between the regularly scheduled 6 month visits, although we expect this to be quite uncommon, if it occurs at all.

In addition to the semiannual follow-up visits, there will be follow-up visits with the study nurse at two weeks and four weeks after initiation of the chemoprevention medication or the corresponding control applications, and every two weeks thereafter if still on treatment. Finally, there will be follow-up by phone with the study nurse, and evaluation of medical records.

A. Baseline assessments

At baseline, all participants will have a full body skin examination by a study dermatologist, as is standard care but also to determine whether the potential participant meets criteria to be in the study. Any skin cancers on the face and/or ears will be removed prior to randomization. Participants will be eligible for participation in the study 30 days after completion of therapy for the skin cancer(s). For the purpose of this study actinic keratoses on the face and ears will be assessed as described in III.B.3. The dermatologist will also review medical records as needed (generally, the patient’s electronic VA record) to insure criteria are met for randomization, and to verify the complete count of skin cancers diagnosed in the prior 5 years with location and diagnosis of each. Copies of pathology reports of all skin cancers diagnosed in the past 5 years will be reviewed by the study chairman’s office to confirm consistent application of inclusion criteria and consistent counting and classification of prior cancers.

The study nurse will administer the baseline interview to capture key data on variables that will be used in later analyses including key predictors of BCC and SCC risk, such as prior skin cancers, sun sensitivity, residential history, use of sun protection, NSAID use, family history of skin cancer, and smoking history. Past history of AK treatment will also be assessed, as well as the reaction to that treatment. Appropriate contact information for the participant and an alternate contact will also be ascertained at this time.
The MAVERIC analytic group has programmed a Charlson index that can be extracted directly from the SAS version of the Austin file. In addition, at baseline we will ascertain key predictors of mortality such as the items needed for the recently published mortality prognostic index\textsuperscript{41, 42}.

B. Assessment schedule

Baseline visit:
- Assess inclusion/exclusion criteria (10 mins)
- Review Informed Consent (15 mins)
- Randomization (5 mins)
- Perform complete skin examination (10 mins)
- Baseline Interview to obtain relevant history (30 mins)
- Quality of Life assessments (20 mins)
- Intervention overview (10 mins)
- Baseline photographs (10 mins)

Telephone interview by study nurse (10 min)
- Bi-weekly during intervention phase
- Once every three months during follow up

Brief follow-up visit at 2 and 4 weeks, and every two weeks thereafter if still on treatment
- Brief face/ears only assessment by study nurse (5 mins)
- Study nurse counseling and focused interview (15 mins)
- QOL assessments (20 mins) at 4 weeks
- Toxicity photographs (10 mins)

Follow up visits (every 6 months)
- Complete skin examination (10 min)
- Follow up interview (time since last visit) (15 min)
- If a potential skin cancer is to be biopsied, digital photograph to document precise location; if a surgery has been performed on a KC that had not been photographed, the location will be photodocumented (10 mins)
- QOL assessment at 12, 24, and 36 month visit (10 min)
- Photographs at first 6 month follow-up visit, and at some sites each 6 month visit after marking of AKs.

In order to better illustrate the typical assessment schedule for participants in VA CSP 562, the following tables have been included for review.
Table 1: Typical assessment schedule for a participant in VA CSP 562

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Timing of intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization</td>
<td>0</td>
</tr>
<tr>
<td>Telephone interview</td>
<td>Weeks 1, 3 and if still on treatment weeks 5, 7, 9, 11</td>
</tr>
<tr>
<td></td>
<td>Month 3, 9, 15, 21, 27, 33, 39, 45</td>
</tr>
<tr>
<td>Brief follow up visit</td>
<td>Weeks 2, 4 and if still on treatment weeks 6, 8, 10</td>
</tr>
<tr>
<td>Regular follow up visit</td>
<td>Month 6, 12, 18, 24, 30, 36, 42, 48</td>
</tr>
</tbody>
</table>

Sample Scenarios

Table 2: Assessment schedule for participant who undergoes a cool down period after initiating treatment for 1 week

<table>
<thead>
<tr>
<th>Date</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/3/09</td>
<td>Randomized into study</td>
</tr>
<tr>
<td>1/10/09 (week 1)</td>
<td>Patient stops study medication (14 doses complete); telephone contact; patient begins cool down period</td>
</tr>
<tr>
<td>1/17/09 (week 2)</td>
<td>Patient continues cool down period; brief follow up visit</td>
</tr>
<tr>
<td>1/24/09 (week 3)</td>
<td>Patient continues cool down period; telephone contact</td>
</tr>
<tr>
<td>1/31/09 (week 4)</td>
<td>Patient finishes cool down; study medication restarted at one dose per day; brief follow up visit</td>
</tr>
<tr>
<td>2/7/09 (week 5)</td>
<td>Therapy continues at once per day; telephone contact</td>
</tr>
<tr>
<td>2/14/09 (week 6)</td>
<td>Therapy continues at once per day; brief follow up visit</td>
</tr>
<tr>
<td>2/21/09 (week 7)</td>
<td>Therapy continues at once per day; telephone contact</td>
</tr>
<tr>
<td>2/28/09 (week 8)</td>
<td>Therapy continues at once per day; brief follow up visit</td>
</tr>
<tr>
<td>3/7/09 (week 9)</td>
<td>Therapy continues at once per day; telephone contact</td>
</tr>
<tr>
<td>3/14/09 (week 10)</td>
<td>Therapy complete (56 doses); brief follow up visit</td>
</tr>
</tbody>
</table>
Weinstock, MA: “The VA Keratinocyte Carcinoma Chemoprevention Trial (VA CSP#562)”

<table>
<thead>
<tr>
<th>Date</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/3/09 (month 6)</td>
<td>up visit</td>
</tr>
<tr>
<td>9/3/09 (month 9)</td>
<td>Regular follow up visit</td>
</tr>
<tr>
<td>12/3/09 (month 12)</td>
<td>Telephone contact</td>
</tr>
<tr>
<td>3/3/10 (month 15)</td>
<td>Regular follow up visit</td>
</tr>
<tr>
<td>6/3/10 (month 18)</td>
<td>Telephone contact</td>
</tr>
<tr>
<td>9/3/10 (month 21)</td>
<td>Regular follow up visit</td>
</tr>
<tr>
<td>12/3/10 (month 24)</td>
<td>Telephone contact</td>
</tr>
<tr>
<td>3/3/11 (month 27)</td>
<td>Regular follow up visit</td>
</tr>
<tr>
<td>6/3/11 (month 30)</td>
<td>Telephone contact</td>
</tr>
<tr>
<td>9/3/11 (month 33)</td>
<td>Regular follow up visit</td>
</tr>
<tr>
<td>12/3/11 (month 36)</td>
<td>Telephone contact</td>
</tr>
<tr>
<td>3/3/12 (month 39)</td>
<td>Regular follow up visit</td>
</tr>
<tr>
<td>6/3/12 (month 42)</td>
<td>Telephone contact</td>
</tr>
<tr>
<td>9/3/12 (month 45)</td>
<td>Regular follow up visit</td>
</tr>
<tr>
<td>12/3/12 (month 48)</td>
<td>Final regular follow up visit</td>
</tr>
</tbody>
</table>

Table 3: Assessment schedule for a participant in VA CSP 562 who undergoes a cool down period after initiating treatment for 2 weeks. As per protocol, the patient has received the minimal dose and treatment is not restarted.
C. Specific assessments

1. Lesion Diagnosis Determined by Central Pathology:

The primary outcome is BCC or SCC treated with surgery. For the purpose of this research, the diagnosis of SCC and BCC will be defined (blind to treatment assignment) by assessment of the central pathology panel because of (1) the critical importance of the primary outcomes, and (2) concerns about consistency of diagnoses across centers and (3) the variable experience and training of the pathologists in centers likely to be involved in this study. Many of these centers rely on pathologists who are not board certified in dermatopathology or who may have diagnostic criteria (for SCC in particular) that might be outside of the mainstream.

All skin biopsies will first be reviewed locally for diagnosis according to the standard of care for skin biopsies. All lesions on the face and ears will then be sent for central dermatopathologic review for study purposes. Standard dermatopathologic criteria (see Appendix A) will be used by our central dermatopathologists, and we will periodically reinforce use of these criteria and evaluate test-retest reliability (see below and section IX.A). The central dermatopathologists will not be aware of the local diagnosis for these lesions.

Our central pathology review for study purposes will be by a panel of 3 board-certified dermatopathologists who will each read the same slides. They are blinded to treatment group. A lesion will be considered a KC if at least 2 of the panel members diagnose it as a KC. The dermatopathologists will review a training set of slides to insure a higher degree of interrater reliability.

After initial review of a lesion by the local site pathologist, slides from all biopsies from the face or ears will be sent to the coordinating center for random distribution to the reference dermatopathologists. A barcode will be placed on the slide and its corresponding biopsy form 20 for tracking purposes. Slides will be packaged in slide boxes, bubble wrapped for mailing and sent in batches of 25 by Federal Express to the specified central dermatopathologist for review. After the review, the dermatopathologist will complete a Form 21 and return both the slides and the corresponding forms to the coordinating center by Federal Express. Slides will then be returned to the local VA where they originated. A 10% random sample of slides will be selected for independent blind rereading by the panel 1 to 2 years later. Some additional slides will be retained for the next quarterly dermatopathologic review.

When there is disagreement between the central dermatopathology panel and the original diagnosis, the treating clinician will be informed of the discrepancy so that he/she can
appropriately care for the patient based upon the total clinical picture and his/her best medical judgment.

2. **Clinical (in-person) examination:**

After the baseline visit, there will be visits with only the study nurse at 2 and 4 weeks after initiation of treatment, and every 2 weeks thereafter until treatment is complete, to reinforce compliance, assess symptoms by self-report, and evaluate erythema and inflammation. These follow-up visits will be important for assessment of acute effects of the chemopreventive treatment and reinforcing counseling on proper use of medication. Besides the personal attention that this provides, this allows the primary investigator at the site to remain blinded to the treatment group. If at any time during the first six months a patient needs to see a dermatologist, one who is unblinded to the study will be made available to them. Participants will then be evaluated every 6 months by a blinded study dermatologist to assess skin lesions. At many VA sites dermatologists routinely take digital photos of lesions during patient visits to create more objective means of detecting new lesions and to assess changes in existing lesions. For the purpose of the study and with the patient’s consent, digital photographs will be used to document lesions as noted above. All patients who give permission will be photographed at baseline and at the 6 month follow-up, as well as during intervention. Photographs of any suspicious lesions that develop during the course of this study will also be taken. At some sites, photographs may be taken at all of the semianual visits after marking actinic keratoses. A central photographic registry will be constructed by the MAVERIC CSPCC in a secure and encrypted manner. Photographs will be uploaded through the Sharepoint System and stored electronically within the study patients’ electronic record. If the local VAMC routinely takes photographs as part of dermatology visits, these photos will also be placed in the local patient medical record as standard practice for that VAMC. Patients will also be asked to consent to the use of these photographs in study related manuscripts and educational materials for healthcare providers. If they refuse to have their photographs used for these purposes or refuse to have photographs taken of their face and ears, they may still participate in the study.

3. **Telephone Contact:**

The study nurse at each site will speak with each participant once per week by telephone during the treatment if no visit is scheduled that week, and once every 3 months at other times if no study visit is scheduled that month (note that study visits are scheduled every 6 months, so this means one phone call between each pair of study visits). The purpose for the weekly calls is to enhance and monitor compliance with treatment and respond to any participant questions. These weekly phone calls during treatment will also be important for monitoring complications of the chemopreventive treatment and providing rapid feedback (at least weekly during the intervention phase) to study leadership and the data and safety monitoring committee regarding any complications, hence to allow changes to be initiated in a timely manner. The purpose of the every 3 month phone calls is to address any issues that may have arisen, assess any potential interval dermatologic or surgical care, and insure appropriate follow-up at 6 month intervals. This will enhance rapport between the
participant and the study nurse, and hence improve retention and adherence to study procedures.

4. **All contacts:**

At all patient visits and at all phone contacts during the first 6 months, participants will be asked to rate the following anticipated side-effects as none, mild, moderate, or severe, with specific reference to the face and ears: (a) redness; (b) itching; (c) burning; (d) soreness/tenderness; (e) crusting/erosions; (f) scaling/flaking; (g) swelling. In addition, at each of these contacts we will ask for the participant’s global assessment of the side effects of the treatment.

5. **Criteria for histopathologic evaluation:**

All lesions biopsied or excised will be submitted for local histopathologic diagnosis in accordance with usual procedures at the clinic, but then the slide will be sent to the data coordinating center for assignment to the reference dermatopathology panel for evaluation, and that evaluation will include the diagnosis which will be used for study purposes. If the panel has already diagnosed a slide from that lesion as KC, they will not be sent additional slides from that lesion (e.g. from a re-excision). We should note that any visible signs of 5-FU treatment (such as erythema or crusting) will have resolved before the first 6 month return visit. The ultimate diagnosis of BCC or SCC of surgically obtained tissue will be by the central reference dermatopathology panel.

6. **Procedures for assessment of AKs:**

The study dermatologist examines each participant semiannually for the primary purpose of detection of any KCs that might be clinically apparent anywhere on the body. At that time they will also assess AKs on the face and ears by multiple methods. The primary method will be to count AKs greater than 5 mm in diameter. This is a method that has been demonstrated to be reliable. We will also assess by two other methods that are widely used or published for the purpose of determining their concordance with our primary method. The first of these is a simple count of all AKs regardless of size. The other is a procedure for assessing surface area covered by AKs as determined by the visual approximation technique that was described by Atkins et al. We will include AK assessment in our training/start-up meeting of investigators prior to the initiation of the trial and regularly over the course of the trial.

7. **Measurement of cream used:**

All tubes will be returned at the end of treatment to the study nurse. Study medication will be returned to the local pharmacy to allow for measurement of the amount of the intervention cream remaining, and thereby an estimate of amount used.

8. **Procedures for ascertainment of deaths:**
Deaths will be ascertained from the VA Vital Status File at the VA Austin Automation Center. This file allows for complete ascertainment as it pulls data from multiple sources, including: the BIRLS (Beneficiary Identification and Records Locator Subsystem) database, the DMF (Death Master File) from the Social Security Administration, and the National Patient Care Database. Deaths will also be noted by the study nurse at each site when they pull up the medical record to determine an appointment for a study visit for the participant that coincides with another visit to the VA medical center. If more information is needed on cause of death than is available in the VA medical record, a death certificate will be obtained.

VII. ECONOMIC ANALYSIS

A. Design Considerations for the Economic Analysis

There are two components of the proposed economic analysis. First, we will conduct a cost-effectiveness analysis from both a VA and a societal perspective. Second, we will conduct a business impact, or cash-flow analysis from a VA perspective. The purpose of this second analysis will be to provide VA managers with the information that they need to accurately determine the financial impacts of adopting the study protocol as standard therapy. Both of these analyses are conditional on the main outcome of the study being an effective intervention. If the intervention doesn't work, the economic analyses are moot, as the intervention will not be clinically adopted.

Skin cancer is a condition for which the treatment can be clearly separated from the treatment of other conditions. Thus, this study will not consider other health care costs; we will assume that the randomization equalizes these across the two study arms. The one exception to this is if a skin cancer metastasizes to another site. The costs and utilization associated with the treatment of metastatic cancers will be considered, conditional on site investigator verification that the metastatic cancer is related to BCC or SCC.

Preliminary calculations based on the effect sizes that the study is powered on project a cost savings associated with the intervention. Further, these cost savings will persist for a wide range of assumptions about the costs of therapy and the effectiveness of the intervention. Thus, there will only be conditional collection of health utilities information. If the initial analysis at the end of the trial shows that we need to value the relevant health state utilities, we will submit a supplemental proposal to CSSMRB for the collection of health utilities.

Study information from the skin cancer-specific quality of life measures collected during the study, will be used to determine the health states that need to be valued. Community ratings will be obtained for these health states. Since study subjects are not required for this method of utility assignment, the collection of the utility data can be deferred without jeopardy to the proposed analysis.

B. Sources of Cost and Utilization Data
VA costs will be captured from the VA Decision Support System (DSS) National Data Extracts (NDEs). DSS is a comprehensive, activity-based hospital accounting system that VA uses to track its costs. Summary extracts are made from this system that track inpatient, outpatient, and pharmacy costs. These data are extracted and converted to SAS datasets at the VA Austin Automation Center (ACC) on an annual basis. They are usually available in February of each year.

Encounter data with ICD-9-CM codes for all encounters, and CPT codes for outpatient encounters are also available from the National Patient Data Base SE file at the ACC. These data will allow centralized tracking of all VA patient care encounters.

At many VA facilities at least some of the skin cancer-related care (especially Mohs surgery) is provided as contract care. To ensure complete data for this care, each site will be asked to identify the types of care that they routinely provide under contract or fee-basis care. Study forms will be used to capture the CPT codes for all fee-basis and contract care. While there are centralized databases of fee basis care, these data have never been carefully assessed for completeness. Further, starting in FY 2007, all fee-basis and contract care is supposed to be captured by DSS. Once the FY 2007 DSS extracts are available in early 2008, HERC will compare the data reported on the study forms with the fee-basis and contract care reported in DSS. If the DSS is found to accurately capture these data, use of the study forms for contract and fee-basis care will be discontinued.

C. Non-VA Health Care

Prior experience from CSP #402 found that 99% of the KC-related care was VA provided. Thus, while patients will be asked to self-report their use of related care obtained from a non-VA provider, the impact of errors of patient self-reporting will be minor. At enrollment, patients will be asked to bring copies of the billing statements for any non-VA skin cancer-related care to each subsequent follow-up visit. At each follow-up visit, the site coordinator will ask the patient if any non-VA skin cancer-related care was received since the last visit. If the patients does not provide copies of the billing statements, the site coordinator will use a study form to determine what non-VA care was provided. Fortunately, there are only a few types of patient care encounters that are relevant care. Thus, the study form will list each of the types of service. VA averages for these types of encounters will be used to assign costs to these encounter types. Patients will also be asked for the date of service. These self-reported uses of non-VA care will be cross-checked with the VA databases, especially the fee-basis files, to prevent double counting.

Patients will also be asked at enrollment if they are currently enrolled in Medicare (median age for CSP #402 was 71). If they are not currently enrolled in Medicare, they will be asked if they expect to enroll in Medicare during the study period. The consent form will include permission to access Medicare records. A finder file of all study patients will be submitted to VIREC, which is the VA repository of the Medicare data for users of VA care. These Medicare data will be used as a further check for study relevant non-VA health care utilization. Given the lag in the linking of the Medicare data to VA users, the Medicare data may not be available for the last year of the study at the time of analysis. But, the Medicare
data will provide data for earlier years of follow-up and allow the assessment of the completeness of the patient self-report of use of non-VA care.

D. Assumptions for Preliminary Cost Analysis

The VA cost of 5-FU was obtained from the April 2007 list of current VA drug prices maintained by the VA Pharmacy Benefits Management (PBM) group. It was assumed that two 40g tubes of 5-FU would be sufficient for each course of chemo-preventive therapy. The April 2007 cost of a 40g tube of 5-FU was $80.42, yielding a per treatment cost of $160.84. The CPT codes were identified for Mohs facial surgery, and the 2005 VA frequency of use of these codes identify their relative use in VA. Using 2006 Medicare RVUs, conversion factors, and APC facility payment rates, we calculated an average cost of $830. This cost decreases to $715 if the surgery is done in conjunction with one of the more expensive types of reconstructive surgeries due to the facility payment methodologies for ambulatory surgery.

To estimate the VA costs for reconstructive procedures, we examine the “repair” codes recorded in VA encounters where Mohs surgery was performed. We used the weighted average of these payments, with adjustments for the Medicare facility payment methodology to obtain a weighted average VA cost for Mohs surgery and reconstruction of $1573.

Based on the information from CSP 402 and a search of centralized VA data, we know that the patients who will be enrolled in this trial have a high incidence of AK, which will almost always be treated with cryosurgery. Again, we used the actual VA use of CPT codes to calculate a weighted average cost for a cryosurgery of $138.

While it is possible that the intervention will reduce other VA costs of care, no other potential savings were included for this preliminary analysis. We acknowledge that there will probably be some added costs of the intervention for following up with patients by telephone during the intervention period. These will be captured during the actual analysis, with care to make sure that they exclude the additional visits/contacts that were part of the research project, not actual patient care. The cost of the initial visit at which the 5-FU is dispensed will not be included as this would be done at a regularly scheduled annual encounter for these high-risk patients.

From the power calculation of this trial, we are conservatively projecting an absolute reduction of 10% in the number of KC that will require surgical treatment. For the base analysis, we also assumed that on average, 0.75 cryotherapy treatments per patient would be averted. This is a fairly conservative assumption, given that 5-FU is known to be an effective therapy for AK and the study patients average more than 1 AK per year, with an average follow-up of 3 years. These assumptions result in a net savings of $116.

We also tested the sensitivity of these assumptions. If no reductions in AK therapy are assumed, the net effect, due solely to the reduction in Mohs surgery is a cost increase of $13. With the 0.75 cryotherapy treatments averted per patient for the treatment of AK, there are net savings as long as the reduction in the need for surgical treatment for facial KC is greater
than 3.6%. Net savings also remain with 0.5 cryosurgeries averted per patient as long as the reduction in surgical treatment for facial KC is at least 5.8%.

E. Cost-Effectiveness Analysis

The cost-effectiveness analysis will be an intent-to-treat analysis, using an incremental cost-effectiveness ratio, and a societal perspective. All costs and benefits will be discounted at a 3% rate. We will monitor the development of the emerging concept of presenting the results in terms of a net health benefit, and will consider this method as an alternative for presenting the results. Essentially, we are acknowledging that this new method could change the consensus on how to report cost-effectiveness studies, and that we will be sensitive to this possibility.

Because this is a VA trial, the cost-effectiveness analysis will be repeated from a VA perspective. This will be done by revising the final analysis to only include the costs directly incurred by VA. This will have no affect on the QALY expressed benefit to the study subjects.

Given the strong prior that the study results will show the intervention to be effective and have a net cost savings (i.e. strong dominance), the utility/QALY assessment will be conditional. The changes in net health utilities associated with the different therapies in this study are likely to be relatively small. Standard indirect utility instruments such as the HUI and the EQ-5D are unlikely to be sensitive enough to detect these changes. The study will regularly collect data using disease-specific quality of life instruments. These instruments will provide sufficient information to allow the characterization of the health states that are most relevant to the study. If the initial analysis at study close-out shows that the net costs of the intervention may be positive, then supplemental funding will be requested to allow the outcomes from the disease-specific quality of life instruments to be mapped to utilities. These utilities will be assigned using a community sample of healthy adults. The study economist has prior experience with this method; he worked with colleagues at Stanford University to obtain community-rated utilities for the Activities of Daily Living scores that were used to measure patient functioning for Geriatric Evaluation and Management patients in CSP #006. Application of this method will allow utilities to be assigned to the disease-specific quality of life measures that will be recorded for study subjects at regular intervals. The advantage of this approach is that it avoids the significant expense of assigning utilities to health states unless it is necessary for the completion of the analysis. It is unlikely that this step will be required, given the preliminary analysis found cost savings at differences in KC surgery rates down to differences that were so small that the intervention would not be considered more effective than current practice.

We also acknowledge the possibility that the interventions have differential effects on patient quality of life that could be the opposite of our expectations. The intervention will treat all patients to prevent the occurrence of KC in some patients (the intervention will also prevent the occurrence of AK in a larger fraction of patients). Thus, all of the intervention patients will experience some disutility associated with the treatment, while only a subset will receive the utility benefits of averted KC or AK. While the hypothesis is that the
intervention arm will result in net higher disease-specific quality of life ratings, we will examine the results to confirm this. If the results of the disease-specific quality of life ratings don’t clearly show a net benefit to the intervention arm, this would also trigger the collection of utilities data from a community sample.

F. Cash-Flow Analysis

The VA is operated on a fixed global budget. VA managers must make decisions on where and how to allocate fixed resources. While traditional clinical trials results can make a compelling case about the effectiveness of an intervention, they don’t provide all of the information that managers need to implement the adoption of new technologies or treatments. Even if this study has the expected outcome of a net savings attributable to the intervention, this alone will not provide sufficient information for VA managers. This is because the study intervention requires an up front investment in chemo-preventive therapy. The up front costs will not be fully recouped in the first year. To allow VA managers to adequately plan for the adoption of chemo-preventive 5-FU therapy, we also plan to use the study data to calculate the expected cash flow affects of implementing the study intervention. We will use the actual utilization of care for patients in the control arm of the study to project when the averted treatments would have occurred, in terms of months since initiation of 5-FU treatment. These will be summarized on a quarterly basis, and compared with the cost of 5-FU therapy.

HERC has planned to include this type of cash-flow analysis in other CSP trials that are already in progress. The intent is to work with various VA leadership organizations to help disseminate this information. If this trials shows the intervention is effective, we will build on these previous management dissemination efforts. The purpose of this type of analysis is to make the results as useful as possible for VA managers. Feedback from this type of effort for other CSP trials will be incorporated into the exact dissemination plan.

VIII. HUMAN SUBJECTS

A. Consent Procedure

After a patient has been deemed eligible for the trial through screening and has demonstrated decisional capacity informed consent will be sought. Ultimately, the participating Site Investigator will obtain permission from the patient. The study coordinator at each site will introduce and explain the study to the patient and present him/her with the detailed consent form and supplementary material to read and review. Subsequently, the participating investigator (or a designated physician) will review and discuss the study with the patient and answer any questions that the patient might have.

The general purpose of the study will be delineated. The treatment comparisons will be clearly described. The randomization process and a clear description of what is expected of the patient will also be described. The risks associated with treatments and procedures will also be addressed. The importance of patient confidentiality will be stressed describing the process for maintaining this confidentiality.
The patient will sign the informed consent in the presence of an independent witness not associated with the study. It must be ensured that the patient understands every aspect of the trial, including its risks and benefits, prior to signing the informed consent.

If the patient agrees, his/her consent to participate in the study will be recorded on the Agreement to Participate in Research form (VA form 10-1086 as modified by the VA Central IRB on June 4, 2008, see Appendix B). The original will be placed in the patient’s medical record. Copies of the signed consent form will be provided to the patient, the Research Office at the participating site (if required by the IRB), placed in the patient’s study file, and faxed and sent to the MAVERIC CSPCC in Boston at the time of enrollment in the study.

Informed consent requires that the patient understand the details of the study and agrees, without coercion, to participation in the study. To obtain informed consent, the following information shall be provided to each subject:

- Name of the study
- Name of the Principal Investigator
- Explanation that the study involves research
- Explanation of the purpose of the study
- Explanation of the treatment procedures
- Description of randomization.
- Description of the risks and benefits of participation in the study
- A description of alternatives to participation in the study
- Explanation that all records will be kept confidential, but that records may be examined by representatives of the VA and/ or the FDA
- Whom to contact for questions about the research and about subjects’ rights.
- Whom to contact in the event of research-related injury.
- A statement that participation in the study is voluntary and that a decision not to participate or to withdraw from the study after initially agreeing involves no penalty, loss of benefits or reduction in access to medical care.
- A statement that the treatments provided as part of this study are free.

Merely obtaining signature consent from the patient does not constitute informed consent. However, the use of a standardized consent form aids in assuring that subjects receive adequate and consistent information about the trial and have consented to participate.

In conjunction with the informed consent procedure patients will review and be asked to sign the Authorization for Release of Protected Health Information From as required by HIPAA.

The participant will be asked to sign a separate consent for the taking and use of full face photographs, to include the ears. This will be documented on VA Form 10-3203, Consent for Use of Picture and/or Voice.

B. Surrogate Consent
No surrogate consent will be allowed.

C. Risks and Benefits

Any procedure has potential risks. The procedures used in this study may cause all, some or none of the risks and side effects listed. There is also the potential for rare or unknown risks occurring. Each study participant will be informed if any new information is developed during the study that might affect their willingness to continue to participate.

Study Cream Side Effects:
Common localized side effects of the study cream include a burning feeling and redness where the medicine is applied, increased sensitivity of the skin to sunlight, soreness or tenderness of the skin, itching, oozing, an open or crusted over ulceration or spot on the skin, a widespread skin rash in the area where the medicine is applied. The study cream may occasionally cause darkening of the skin or permanent scarring, although scarring is rare.

Triamcinolone “Cool Down” Cream Side Effects:
It is very unusual to have any side effects from the Triamcinolone cream, but it can rarely cause burning, itching, irritation, dryness, or a secondary infection.

Possible benefits of this study may include prevention of future skin cancers for patients who receive the active treatment. Information learned from this study may help us treat future patients who develop skin cancers.

IX. QUALITY CONTROL PROCEDURES

Standardization/Validation of Measurements

Each site will have two staff dermatologist investigators who will be responsible for all of the skin examinations. Prior to the initiation of the study, all investigators from the clinical sites will meet to review study procedures, including a training exercise to measure and maximize inter-rater reliability of clinical assessments. That session will involve patient volunteers and clinical images. Investigators will independently examine the faces and ears of the patients, note their clinical judgments on study parameters including presence or absence of a skin lesion worthy of biopsy as a potential KC, and including measures of AKs. Any differences in the results of these examinations will be discussed so that a consensus judgment can be reached and all investigators can re-examine the lesions with that consensus judgment in mind.

The study nurses will be trained to collect data for the study prior to and, most importantly at, the study kickoff meeting. They will be trained in the use of study medication and counseling regarding its use. They will be trained in standard responses to all anticipated side-effects of the study creams. They will be given the opportunity to review the protocol and case report forms prior to the meeting. At the meeting, study nurses will be given an
opportunity to review source documents, and to practice administration of the study assessments and interview. Verbal feedback and discussion will follow to ensure that each nurse comprehends the proper methodology for assessment. The meeting will also cover an in-depth review of the study operations manual. Such a review will serve to reinforce the training described above and will orient the study personnel to the reference guides for the study.

The central dermatopathologists will meet quarterly to review a selection of slides read in the prior 6 months that were not selected for the test-retest assessments. They will independently grade these and then discuss those on which they differed in any assessment.

Patient Management

For CSP 562, the site investigator at each site will be responsible for the management of his/her patients. If the patient misses a treatment visit or an assessment, the study nurse will contact the patient to reschedule the visit. Every effort will be made to accommodate the patient schedule and safety concerns.

Protocol Deviations

Documentation of any protocol breaches will be required. A Protocol Deviation form will be created by the MAVERIC CSPCC to ensure the proper tracking of events. Each protocol violation will be evaluated by the study chair, and a determination made regarding the validity of any justification for the violation. Any medical center or subject with repeated protocol violations in the absence of valid justification, and after remedial protocol training, will be recommended for termination to the Data Monitoring Committee (DMC). If any member of the DMC or the monitoring bodies for CSP 562 feel that adherence to the protocol will be detrimental to a participant’s health or well being, the interest of the participant will take precedence and the subject will be withdrawn after consultation with the executive committee.

Site Performance Monitoring

Strict adherence to the protocol will be monitored by the Data Monitoring Committee, the Executive Committee and the Study Group. By agreeing to participate in the study, the medical center delegates responsibility for global monitoring of the ongoing study to the Data Monitoring Committee, the Cooperative Studies Program Coordinating Center’s Human Rights Committee, the Cooperative Studies Scientific Merit Review Board (CSSMRB), the MAVERIC Cooperative Studies Program Coordinating Center (MAVERIC CSPCC) in Boston, the VA Central IRB and the Albuquerque Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC). However, the Research and Development (R&D) and the Human Studies Committee of the local medical center may require the investigators to submit additional reports concerning the status of the study.

Probation/Termination of Participating Centers
The recruitment rate and operational aspects of this study will be monitored continuously by the Study Chairman and CSPCC. Medical centers will only continue participation if adequate recruitment and proper procedures are maintained. Termination of a center will only be taken by the Executive Committee with the concurrence of the DMC and the Director, Cooperative Studies Program.

X. DATA MANAGEMENT AND DATA SECURITY

The MAVERIC CSPCC in Boston will manage the trial data for CSP #562 using a web-based Electronic Data Capture (EDC) system. The system allows site coordinators to enter patient data directly into a web-based database and thus manage their patients, handle data clarifications, and correct patient data online. The data entered onto these forms goes directly into the study database. Parallel paper case report forms (CRFs) will be provided to site coordinators as guides for data collection. Patient questionnaires will use paper forms as a primary means of collecting data. These surveys will be faxed to the Boston CSPCC (MAVERIC) and will be entered directly into the database. This system is designed to make the process of patient data management easier, timelier, and more efficient. The software that will be used by the MAVERIC CSPCC utilizes MS InfoPath forms on a SharePoint platform. Accessing the system requires a VA intranet connection and a browser.

After the study is approved, the Study Chairman and Study Director will prepare an Operations Manual for site staff to guide them through the operation and management of the study and data collection tools. A training session will occur at the study kick-off meeting for all investigators and coordinators to assure uniformity in patient management, data collection, and study procedures. At training, coordinators will be provided with reference materials on the software tool and tasks. Once formal training is completed, user accounts utilizing a URL specific to the study to access and use the system and enter patient data will be activated. Accounts are password protected and are unique to the users' functional study group (i.e. those for a site coordinator would differ from those of the coordinating center or site monitors). Formal training on the use of the InfoPath/SharePoint system for clinical study management will also be provided. Systems training will also be held at annual meetings, and on an as-needed basis for new study personnel.

For CSP 562, MS InfoPath/SharePoint designers will create a study-specific database that includes case report forms, visit schedule, and data queries. Data clarifications (DCFs) or data queries will be managed in two ways. Certain queries will be programmed into the forms that are designed to fire upon data entry. Additional DCFs will be programmed using other data analysis tools such as SAS and will be uploaded into the system for site coordinators to address. Furthermore the system will allow manual DCFs to be entered into the forms by the coordinating center as needed. Updates to the electronic forms and database can be generated during the study without impacting collected data. Study reports can be generated from exported data in order to track the study progress and to monitor adverse events, in particular Serious Adverse Events. Study reports will be circulated to appropriate members, including the Principal Investigators, the Study Chairman, and the Data Monitoring Committee.
The goal of the MAVERIC CSPCC program is to develop a MS InfoPath/SharePoint electronic data capture tool that is fully compliant with US Federal regulations regarding electronic web based data capture systems established by the Food and Drug Administration under 21 CFR 11. Data entered directly into the database provides the official clinical record for data collection. Source documentation is handled in the same manner as a paper based system. All paper based records will be kept under lock and key. Electronic transmission of these records will occur via secure fax. The MS InfoPath/SharePoint electronic data capture system will be validated by the MAVERIC CSPCC Quality Assurance Team to ensure the integrity of the data capture software.

The servers housing the study databases will be located at a secure VA facility. This facility has yet to be determined but the one chosen will support round the clock web services and monitoring within a secure VA environment in order to provide an optimal infrastructure for the protection of sensitive information. The clinical database with all research data will be housed behind the VA firewall on VA owned and maintained servers. Accordingly, the information housed within the MS InfoPath/SharePoint system will be afforded the same level of security as all forms of VA protected and/or highly sensitive information. Additionally, the system will be monitored by the MAVERIC Quality Assurance and Information Technology teams to ensure that all applicable VA regulations and directives are strictly followed.

Backup copies of the database will be transferred behind the VA firewall to the MAVERIC CSPCC on a frequent basis depending on the study need (at least once per day). These backup copies will be transferred and stored across secure connections according to VA regulations and MAVERIC CSPCC operating procedures. Periodic off-site back-ups will be made as part of a comprehensive disaster recovery plan. The Director of Information Technology, will ensure that backup media are stored in compliance with all federal, and VA regulations on the storage of potentially sensitive information. The Director of Information Technology will also ensure that all backup media is encrypted in compliance with the current best practices established and approved by the Center Director(s). Encrypted backup media will be stored in a physically secure location with access restricted to essential personnel. Access to back-ups may be at the discretion of the Center Director(s) and/or the Director of Information Technology.

Access to the study data is heavily restricted to individuals with CSP approval to access the data. Individuals must be properly credentialed research staff and must be compliant with VA security trainings (i.e., Research Data Security, HIPAA and VA Privacy Training, Cyber-Security, and Good Clinical Practices). In addition, research data will be stored on VA secure servers with restricted permissions for copying and exporting data. Only properly approved Coordinating Center personnel will have the ability to copy and export data. These individuals have received training on the local SOP governing their permissions and will not access or export data without written approval from the Coordinating Center Director. Furthermore, the permissions of the electronic systems are structured such that individual sites can only see the data for their study participants, and they cannot see or access the data for another clinical site or for another participant.
Access to PHI will be heavily restricted to individuals approved by CSP to have access to the data. Approximately 18 people in total will have access to some form of PHI for the study.

At the Clinical Sites a total of three people will have access to PHI. These individuals will be able to access all forms of PHI.
1. Principal Investigator
2. Co-Investigator
3. Nurse Coordinator

At the Coordinating Center a total of six people will have access to PHI. These individuals will be able to access all forms of PHI.
1. Project Manager
2. Data Manager
3. Biostatistical Staff (junior biostatistician and senior biostatistician)
4. Quality Assurance Officer
5. Project Director

At the Pharmacy Coordinating Center a total of six people will have access to PHI. These individuals will be able to access de-identified forms of PHI.
1. Clinical Monitors (3 in total)
2. Study Pharmacist
3. Adverse Event Specialist (Regulatory Affairs and Safety Officer)
4. Pharmacy Project Manager

Research data will only be stored on secure VA servers within the VA firewall. Data will not be stored on desktops or on University affiliate servers. Study data will be coded with a unique study identifier for each participant and stored in a de-identified manner. Identifiable information will be collected for patient tracking and safety purposes, but will only be kept for as long as the study is active. De-identified clinical data will be stored separately from the participant’s name, contact information, and real SSN. Access to the cross-walk file linking the participant’s identifiers and their study data will be restricted to the clinical site and to the project manager at the coordinating center. This file will be destroyed according to CSP policy.

When the study is on-going, the electronic data capture systems will utilize state-of-the-art technologies in order to protect the data during transmission. All of these technologies exceed the current VA standards for transport. In brief, electronic systems will employ secure socket layer technology and FIPS 140-2 compliant encryption algorithms to ensure that data is not vulnerable during transport. In addition, all data will be stored within the VA firewall and will be password protected at all times. Hard copy data will be sent via a traceable mail system (i.e., FEDEX), via a courier, or via secure fax. Faxes are electronically routed to document management systems housed on VA protected servers located at the Regional Data Center in Philadelphia, PA. Access to these secure fax servers is restricted to the Coordinating Center personnel with approved access to the system. All secure fax
servers are compliant with VA directive 1605.1 and 6500. All data security incidents will be reported in accordance with VA policy within one hour of discovering incident to:
1. The District (local) Information Security Officer (ISO)
2. The MAVERIC Data Security Officer
3. The Central IRB
4. the appropriate local IRB.

Quality control checks and clinical monitoring will enable the Coordinating Center to surveill the study database and the clinical sites to ensure that the data have not been improperly used or accessed. 21 CFR part 11 compliant audit trails and access logs will be checked routinely. In addition, the clinical monitors will provide continuing education on good clinical practices and will check all clinical site operations for violations of data security policies and best practices.

The clinical data for VA CSP 562 are considered property of the Cooperative Studies Program and shall not be sent off-site (i.e., outside of the VA) without expressed written permission from the CSPCC Center Director and CSP Central Office approval. All data transfer and data security policies of the VA, the Cooperative Studies Program, the MAVERIC CSPCC, and the local healthcare system will be closely followed. The MAVERIC Quality Assurance team will work closely with the local research compliance officer, the information security officer and the VA privacy officer as needed to ensure that data security and data transfers are handled appropriately.

Retention and destruction of data will be conducted according to CSP operating procedures and federal and local VA regulations. This will include data stored at the MAVERIC CSPCC and at the VA facility housing our servers. Identifiable data will be kept according to CSP policy as outlined in the “CSP Guidelines for the Planning and Conduct of Cooperative Studies.” Specifically, identifiers will be kept on site at the MAVERIC CSPCC for a minimum of five (5) years or as dictated by the FDA or other regulatory agency with specific written procedures (i.e., 2 years after last approval of a marketing application, etc). At the end of the record retention period, the CSPCC will conduct a review to determine if it is appropriate to archive the study data. If it is determined that the study data must be kept active, the CSPCC will retain the database in its entirety until the primary and secondary analyses are completed. At the completion of analyses, study data will be de-identified and stored indefinitely. If, however, the study is archived, the study data will be de-identified electronically and stored indefinitely.

XI. BIOSTATISTICAL CONSIDERATIONS

The study will enroll a total of 1000 patients, 500 of whom will receive the topical 5-FU-based treatment, and 500 of whom will receive the control treatment. We will enroll 500 patients per year for two years to accrue 100 patients per site at 12 VA medical centers. The outcome measure distinguishes between surgical excisions of a pathologically confirmed KC lesion (either BCC or SCC lesion) and the rare excisions that result in any
other diagnosis. Because chemoprevention may have no effect on other lesions, only KC lesions will be counted for the primary outcome. The primary outcome measure is:

The time after enrollment in the study until the first diagnosis leading to surgical treatment of a pathologically confirmed KC lesion.

In terms of the alternative hypothesis we wish to show that:

The 5-FU-based field treatment strategy is effective in the prevention of surgery for a pathologically confirmed KC lesion.

A. The Primary Outcome:

The null hypothesis is that the two treatment groups (5-FU intervention and control therapy) do not differ in their time-to-event hazard rates. The alternative hypothesis is that intervention has a lower hazard rate than control therapy with a hazard ratio for control therapy compared to intervention exceeding 1.42.

This four-year study will enroll patients for 2 years so that the last patient enrolled will potentially have up to 2 years of follow-up. The first patient enrolled will potentially have up to 4 years of follow-up. On average, patients will potentially have approximately 3 years of follow-up. Thus, the power calculations are based on estimates of a surgically treated diagnosis of KC within 3 years.

Based on the VATTC study we expect the 3-year rate of diagnosis (but not surgical excision) of a pathologically confirmed KC lesion will be 49%. This follows from fitting a simple exponential curve to the rate of diagnosis, setting the 5-year incidence rate at 69%, and interpolating the 3-year incidence rate of 49% (see section IV: Inclusion criteria).

Instead of 49%, we have chosen a 3-year of 42% for the outcome, surgical excision of a pathologically confirmed KC lesion. We make this absolute reduction of 7% for several reasons. First, as noted in Section III.A, only 91% of diagnosed KC lesions were surgically excised in the VATTC study. This reduces the absolute rate by 5% from 49% to 44%. Second, a rare patient who developed both a SCC and a BCC at the same time will only be counted once. Third, in the proposed study, the 3-year incidence rate for KC may be slightly reduced because of differences between the old VATTC protocol and the proposed protocol. In the proposed trial physicians will adhere to their internal policies and tend to systematically remove many AK's with cryotherapy and thereby may lower the 3-year KC rates. In the VATTC trial, centers were asked to take a watchful waiting policy on most AK's, but tended to follow their own internal policies on this matter. Fourth, for the proposed trial we will exclude patients who had topical field therapy with 5-FU during the 3 years prior to enrollment, and we speculate that these patients may be at higher risk for KC's than the eligible patients.

Under the null hypothesis:
Weinstock, MA: "The VA Keratinocyte Carcinoma Chemoprevention Trial (VA CSP#562)"

The three-year KC surgery rate will be 42%

Under the alternative hypothesis for patients treated with 5-FU:

The three-year KC surgery rate will be 32%

The reductions attributed to treatment may be viewed in several ways. The absolute reduction from 42% to 32% is 10%, the relative reduction is \((42 - 32)/42 = 24\%\), and the hazard ratio (control hazard rate/treatment hazard rate) of 1.42 midway between the simple odds ratio, \(42(100 - 32)/(32(100 - 42)) = 1.54\) and the risk ratio \(42/32 = 1.31\).

B. Sample Size and Statistical Power Considerations

The results for the KC primary outcome measure, time until first SCC diagnosis, will be analyzed by means of the two-sided log-rank test to detect either a hazards ratio that exceeds 1.42 or is less than \(1/1.42 = 0.74\). The test will have a two-sided 4.8% type I error. (When added to the interim analysis that has a 0.2% Type I error, the overall type I error is 5%).

The test has 90% power to detect a ratio of hazards of 1.42 or larger or 0.74 or less with a total of 1000 patients, 500 per study arm. This assumes that 8% of the patients either die or are lost to follow-up while on-study before a SCC diagnosis can be observed. The power for the log-rank test was computed using Schoenfeld’s formula48.

C. Interim Analysis

We will perform one interim analyses when the first 500 patients (250 in each study arm) enrolled have completed two years of follow-up. Assuming a uniform rate of enrollment over time this interim analysis should take place at the end of year 3. With an 8% loss-to-follow-up rate each study arm will have 210 evaluable patients.

The one interim analysis carried out when the 500th patient completes two years of follow-up has a small effect on overall type I error. The interim analysis has a Type I error of 0.2%. The interim analysis is two-sided, but the interim null hypothesis will only be rejected if the hazard ratio exceeds 2.39. If the hazard ratio is less than \(1/2.39 = 0.42\) then trial will be stopped for futility.

After 3 years the first patient entered will potentially have 3 years of follow-up and the last patient entered will potentially have 1 year of follow. Thus, the average potential follow-up will be two years. If we expect a 42% KC rate at three years then under the exponential model we would expect a 32% KC rate at two years.

Under the interim analysis null hypothesis:

The two-year KC rate will be 32%

Under the interim alternative hypothesis for patients treated with 5-FU:
The two-year KC rate will be 16%

The reductions attributed to treatment may be viewed in several ways. The absolute reduction from 32% to 16% is 16%, the relative reduction is (32 – 16)/32 = 50%, and the hazard ratio (control hazard rate/treatment hazard rate) is 2.39.

We considered earlier times for interim analyses, but rejected this idea because sample sizes on the order of 150 per study arm only have modest power to detect very large effects.

For both the interim analysis and the primary analysis we considered the possibility that the effect of 5-FU merely delays the clinical emergence of a KC by a short period, such as 6 months. Then a wide gap between control and treatment arms, due to lower incidence in the treatment arm, might rapidly narrow with more follow-up. Indeed, this possibility led us to propose to monitor VA electronic records and passively follow patients after the four-year study ends to detect such narrowing. Finally, compared to other types of cancer KC’s are seldom fatal, so that the evaluation of costs to the VA and patient morbidity assume greater importance. We expect that to gather the data for these evaluations would prolong the trial past the early stopping date.

D. Censoring and Losses to Follow-up

We have made a conservative assumption about censoring of KC surgical events due to losses-to-follow. Overall, the VATCC study lost 20% of the subjects, mostly due to death. The VATCC study had an average follow-up of up to 4 years whereas the proposed study has an average follow-up of up to 3 years. As in that trial, participants will continue to be followed through follow up visits and phone calls regardless of their use of study medication. Once enrolled in the trial reasonable effort will be made to retain the participant in the trial. Thus, we expect that 15% = (3/4)*20% of patients will die or be lost-to-follow-up during the proposed 4-year study. Furthermore, we assume that over one half of these deaths/lost-to-follow-ups (8%), will occur before and 7% will occur after a KC diagnosis. In the VATCC study the average age at baseline was 71 years and many patients had serious comorbid conditions as gauged by the Charlson Index. We have accounted for this in item 9 in the exclusion criteria.

In the VATCC trial deaths tended to come later in the follow-up period. Because the proposed study is shorter than the VATCC study, death or lost-to-follow-up rates within two years of baseline should be lower than death or lost-to-follow-up rates between 2 and 4 years after baseline. Because KCs seldom cause death or losses to follow-up, we assume that when a patient dies or is lost-to-follow-up and thereby potentially censors a KC surgical event, the death or loss-to-follow-up is independent of both treatment assignment and disease.

E. Data Analysis Plan
The primary outcome hypothesis will be tested using a two-sided log-rank test to compare the hazard rate for one treatment group to that for another treatment group. A significant difference showing that the intervention strategy compared to the control decreases the hazard of surgery for pathologically confirmed KC will be regarded as a positive result, whereas a result that shows intervention does not significantly differ from or, in fact, significantly increases the hazard rate will be regarded as a negative result. We will report the hazard rates, their ratio and the 95% confidence interval about the ratio. This will be followed by further refined analyses, using multiple linear Cox proportional hazards regression modeling, to take account of the effects of baseline covariates on the primary outcome measure. Covariates will include demographic and clinical factors (age, sex, smoking status, education, number of AK’s, history of BCC, of SCC, or both).

The regression modeling we shall employ will include a model with treatment by covariate terms to explore the possibilities of treatment by covariate effects (that is, exploration of potential subgroup effects). We will test the proportional hazards assumption by including a time-treatment interaction term in the model. We will use graphic methods to study goodness-of-fit.49

F. Extended Follow-Up

The four-year study can be divided into two periods; namely, a 2-year start-up and enrollment period, a 2-year follow-up period in which patients are only followed. Hence, the length of follow-up time may vary from 2-4 years. Assuming a uniform rate of enrollment the average potential follow-up time will be 3 years.

The power calculations account for both the varying amount of follow-up time and for the censoring of outcomes. Varying follow-up time and the length of the recruitment period have negligible effects on power. We have assumed an 8% rate of lost-to-follow-up combining the on-study death rate with the study lost-to-follow-up rate. Hence, the statistical power calculation is based on the 920 evaluable patients among the total of 1000 enrolled.

When the study ends after 4 years we will continue for one year to follow patients by tracking the medical procedures they have as reported in the VA Austin database. We will look for an excess of KC surgical events in the 5-FU treatment arm indicative of events delayed by treatment as opposed to prevented by treatment. We may also wish to contact participants after during this time if we become aware of some medical information related to the study that may benefit them.

G. Secondary Analyses

Secondary analyses are of several types; analyses directly related to the primary hypothesis of BCC and SCC surgical endpoints, quality of life as measured by the Skindex instrument, multiplicity of AK’s, and cost analyses. Cost analyses are described in section VII.

1. Time to surgery for a new BCC and for a new SCC:
In analyses directly related to the primary hypothesis, we will disaggregate KC into its components BCC and SCC. Then we will compare the treatments with respect to each of the two separate outcomes of the time to a diagnosis leading to surgery for a new SCC and time to a diagnosis leading to surgery for a new BCC using the analogous time-to-response analysis delineated for the primary analysis. For this secondary outcome each of the two parallel null hypotheses is that the two treatment groups (intervention and control therapy) do not differ in their time-to-event hazard rates. As in the primary analysis, we will begin with the two-sided log-rank test for each of the two outcome measures, time until the first BCC diagnosis leading to surgical treatment of a pathologically confirmed SCC lesion and time until the first BCC diagnosis leading to surgical treatment of a pathologically confirmed BCC lesion.

We will carry out additional time-to-event analyses of the aggregated KC outcome. We will apply the log-rank test to the data obtained from the extended follow-up beyond 4 years as in the primary analysis. This analysis will be done on both the final data set when the trial ends and on the extended follow-up data set. For each of these analyses we will report the hazard rates, their ratio and the 95% confidence interval about the ratio. This will be followed by further refined analyses, using multiple linear Cox proportional hazards regression modeling, to take account of the effects of baseline covariates on the primary outcome measure. Covariates will include demographic and clinical factors (age, sex, smoking status, education, number of AK’s, and history of BCC, of SCC, or both. The regression modeling we shall employ will include a model with treatment by covariate terms to explore the possibilities of treatment by covariate effects (that is, exploration of potential subgroup effects).

These secondary analyses are exploratory in nature and thus we have not assigned it a level of power. Extensive exploratory analyses will address the issue of the optimal time interval between applications of 5-FU therapy. Assuming that one 5-FU treatment reduces the hazard of surgical outcomes, we will separately study the disease endpoints of BCC, SCC, and KC to determine the shape of the hazard rate over time for the 5-FU treated and control patients. The objective will be to estimate the hazard rate for a new BCC, SCC, or KC in the treated and untreated groups. We will use an extension of the proportional hazards model, specifically with a Weibull frailty model that provides an explicit model for the hazard rate. In particular, we will test whether the hazard rate for patients treated with 5-FU remains lower than the rate for controls over time. A prolonged period of lower hazard rates would indicate the destruction of precursor lesions. Another pattern of interest would be an initial lowering of the 5-FU hazard rate that eventually rises to a higher level than the control hazard rate. This would indicate that 5-FU treatment delays the incidence of new KC’s. Assuming 5-FU is effective, the shape of the hazard function over time will guide us in constructing a schedule for when to re-administer 5-FU.

2. Quality of Life:
We will compare the treatments with respect to the change in the Skindex and Skin Cancer Index scores after one year and after two years. The change after one-year is the difference between the one-year score and the baseline score. The change after two years is the difference between the two-year score and the baseline score. Regarding these changes as
continuous outcomes, we will use Student’s t-test to compare the treatments. Controlling for the covariates listed above we will carry out a linear regression analysis with treatment as the major factor. Confirmatory analysis will be done using combining the one-year, two-year, and three-year change scores into a repeated measures regression analysis. This analysis will treat the factor subject as a random effect and explore the possibility of different sizes of effect within each follow-up year.

3. Burden of Actinic Keratoses:
We will evaluate the effect of study treatment on the burden of actinic keratoses on the face and ears, as assessed by counts of large lesions, >= 5 mm in diameter. For the analyses of counts and for the number of spot treatments we will fix the follow period at two years and carry out a simple Poisson regression comparing the treatments and a more complex Poisson regression comparing the treatments and controlling for covariates. For the analyses of estimates of skin area affected (a continuous outcome) we will fix the follow period at two years and carry out a Student’s t-test comparing the treatments and a more complex linear regression comparing the treatments and controlling for covariates. To confirm this analysis we will collapse the Poisson counts into ordinal categories; none, 1-3, 4-10, 10 or more. We will rerun the analysis using polychotomous logistic regression. For each of the proposed analyses viewing baseline and each follow-up year as repeated measures we will also analyze the data with subject as a random effect using the SAS procedure NLMIXED.

4. Exploratory analysis of endpoint location:
We will review photographs of endpoint lesions to ascertain any particular sub-areas on the face and ears at which the chemopreventive treatment may have been more or less effective. We will partition the face and ears into sub-areas that have a reasonable number of endpoints. We will then compare groups stratified by sub-area in terms of survival analysis hazard rates using SAS Procedure TPHREG, and examine the variation of hazard rate ratio by sub-area.

5. Nonsteroidal anti-inflammatory medications (NSAIDs):
We will assess use of NSAIDs (OTC and prescribed) to evaluate their relation to the risk of KC since that association has been suggested but is controversial. This analysis will merely extend the proposed survival analyses by adding the covariate ‘NSAID use’.

XII. GOOD CLINICAL PRACTICES

A. Good Clinical Practices (GCP) and Site Review Program

The Site Monitoring, Auditing and Review Team (SMART) is responsible to assure that participating sites conduct the study in compliance with Good Clinical Practices. The SMART team will develop study specific tools for the sites and reviewers. The SMART team will provide GCP training at the kick-off meeting and during subsequent on site visits. GCP reviewers will visit participating sites shortly after enrollment is initiated and annually thereafter to monitor investigator regulatory compliance, protocol adherence, and overall research practices. To promote GCP in the trial, SMART develops written GCP guidance and tools specifically for the trial and provides training in the use of these materials and in
the principles of GCP. This training is an ongoing process that is initiated at the time of study kick-off and supplemented during on-site visits. Apart from regularly scheduled GCP review visits, an independent comprehensive GCP site audit may be conducted at any time at the request of study management or site reviewers.

In summary, SMART will accomplish the following:

1) Develop and provide sites with comprehensive study conduct tools including Essential Documents Binders, Patient Study Files, Source documentation requirements to aid in organizing and maintaining records in compliance with the protocol and GCP.
2) Present GCP training at the study kick-off meeting with reinforcement during periodic site review visits.
3) Develop study evaluation tools for site reviewers, including regulatory compliance, and verification of critical data points selected with the aid of the Study Chairman.
4) Conduct site GCP initiation visits to participating sites to aid in implementing the training, practices and tools provided CSPCC and SMART.
5) Conduct review visits to each participating site at least annually monitor investigator regulatory compliance, protocol adherence, and overall research practices.
6) Conduct a final review visit during the last year of study conduct to assure completion of all study tasks and appropriate archiving of study records.
7) Perform independent audits at sites as requested by CSPCC and other members of the study management and oversight teams.

Protection of the rights and welfare of patients is a primary concern of CSP. Informed consent will be documented in this trial by the use of a consent form prepared by each site investigator and approved by the local IRB; the consent form must be sent to the CSPCC before the trial may begin.

All patient data at sites will be stored in locked files. Computers with research subject data will be password protected to ensure confidentiality. The MAVERIC CSPCC is compliant with the Federal regulations regarding electronic web-based data entry systems established by the FDA under 21 CRF part 11.

Prior to the start of any study using DataLabs Clinical, extensive study specific validation will be performed. This process will be documented and placed on file at the MAVERIC CSPCC.

B. Summary of Monitoring and Auditing Plans

Monitoring Bodies

Monitoring the various aspects of the study will be carried out by: the Executive Committee, the Data Monitoring Committee (DMC), the Human Rights Committee, and the Study Group. These committees will meet according to the prevailing practice of the Cooperative Studies Program (at the beginning of intake, nine months later, and every twelve months thereafter). In addition, at the mid-point of the study, CSSMRB will review the study.
The Executive Committee will oversee study operations, the performance of participating medical centers, and the quality of data collected. The members of the Executive Committee will be selected by the Study Chairperson from members of the Planning Committee and Participating Investigators. The Executive Committee formulates plans for publications and oversees the publication and presentation of all data from the study. Permission must be granted by the Executive Committee before data from the study may be used for presentation or publication.

The Data Monitoring Committee (DMC) will review the progress of the study and monitor participant intake, outcomes, complications, and other issues related to participant safety. They will also monitor the assumptions underlying sample size calculations for the study and alert the investigators if they see substantial departures as the data accumulate. The DMC will be composed of experts in dermatology and clinical trials. The Study Chairperson will make nominations to the Director, Cooperative Studies Program (CSP), who will make the final selection for the Board. The DMC will make recommendations to the Director of the Cooperative Studies Program as to whether the study should continue or be terminated. The DMC can consider participant safety or other circumstances as grounds for early termination, including either compelling internal or external evidence of treatment differences or feasibility of addressing the study hypotheses (e.g. poor participant intake, poor adherence). Data on study process will be provided to the DMC by the study biostatistician. The DMC will decide on specific intervals at which to meet. Every six months, the study biostatistician will provide the DMC with an interim summary report on the study status and on safety data for monitoring purposes.

The Human Rights Committee (HRC) will meet every twelve months to ensure that the participants' rights and safety are being properly protected. They may send a representative to the DMC meetings. In the interim, the HRC may be asked to convene if there is any serious event requiring HRC attention. The HRC will be presented with a report from the study biostatistician, or designee, as to the progress of the study and ethical issues relevant to the HRC. In addition, there will be HRC site visits to aid them in determining that the participants' rights and safety are being properly protected.

The Study Group, which consists of all participating investigators, will meet to discuss the progress of the study and any problems encountered during the conduct of the trial.

Clinical Monitors

The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that medications are properly stored and accounted for; verify that subjects consent for study participation has been properly obtained and documented; confirm that research subjects entered into the study meet inclusion and exclusion criteria; and assure that all essential documentation required by good clinical practices guidelines are appropriately filed.
Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and good clinical practices guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

The monitors will verify that study procedures are being conducted according to the protocol guidelines. At the end of the study they will conduct a close out visit to advise the storage of study records and return of unused study medication.

Monitoring Adverse Events and Serious Adverse Events

Timely and complete reporting of safety information assists study management in identifying any untoward medical occurrence, thereby allowing: 1) protection of safety of study patients, 2) a greater understanding of the overall safety profile of the study interventions and therapeutic modalities, 3) appropriate modification of the study protocol, 4) improvements in study design or procedures, and 5) compliance with regulatory requirements.

Role of the Local Site Investigator in Adverse Event Monitoring

The local site investigator will be responsible for the adverse event reporting requirements as outlined below:

a. Reviewing the accuracy and completeness of all adverse events (AEs) reported.

b. Compliance with local IRB policies for reporting AEs and/or serious adverse events (SAEs).

*NOTE: In November 2004, the VA published “Reporting of Adverse Events in Research to the Office of Research Oversight (ORO)” in VHA Handbook 1058.1. Investigators should be aware of this new reporting requirement. This requirement, however, does not eliminate the need for investigators to report both AEs and SAEs to the CSP#562 Sponsor as per the study protocol.

c. Reporting to the IRB safety issues reported by the Sponsor

d. Closely monitoring research subjects at each study assessment visit for any new AE and SAEs.

C. Collection of Safety Information

Adverse Events

Adverse events (AEs) are defined by the ICH for Clinical Safety Data Management (ICH-E2A) as “any untoward medical occurrence in a clinical investigation subject that is subjected to one of the study interventions that does not necessarily have to have a causal relationship with the interventions. An AE, therefore, can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study interventions.”
Adverse events collected in CSP 562 will be those related to the study intervention. Related events involve an assessment of the degree of causality (attribution) between the study intervention and the event. Site investigators will be asked to provide an assessment of relatedness. All adverse events with a reasonable causal relationship to the investigative treatment should be considered “related.” A definite relationship does not need to be established. For the purpose of CSP #562, the study interventions are topical use of 5-FU, and triamcinolone. The study interventions used in CSP #562 are standard treatment regimens currently used in usual clinical practice and have well-characterized adverse effect profiles.

During the study, data on adverse events will be collected spontaneously through patient reports, actively elicited at each clinic visit through open ended questioning and examination, and gathered at the time of telephone contact during the therapy period.

The collection of AE information will begin the day the subject signs the Consent Form and will continue until the end of study participation for each subject. Adverse events related to the study intervention that are reported to study personnel must be recorded on the Adverse Event Form and documented in source records, e.g., the electronic VA medical record and/or the subject’s study record. In this way, the site creates a permanent record that provides information on the subject’s clinical course while in the study.

Adverse events should be followed to resolution or stabilization. AE follow up should be documented in the patient’s source records, e.g., the electronic VA medical record and/or the subject’s study record. AEs should be reported as SAEs if they meet the SAE reporting requirements.

**Serious Adverse Events**

Serious adverse events (SAEs) are a subset of adverse events and are defined by the ICH for Clinical Safety Data Management and CSP Global SOP 3.6.1, as any untoward medical occurrence that:

a. Results in death
b. Is life threatening
c. Requires inpatient hospitalization or prolongation of existing hospitalization
d. Results in persistent or significant disability or incapacity
e. Is a congenital anomaly/birth defect
f. Any condition that, based upon medical judgment, may jeopardize the subject and require medical or surgical treatment to prevent one of the above outcomes

For CSP #562, all serious adverse events will be collected, including those considered related and unrelated to the study interventions. Study interventions are defined as are topical use of 5-FU, and triamcinolone. Serious adverse events with a reasonable causal relationship to the study interventions and associated medications should be reported as “related.” A definite causal relationship does not need to be established.
Serious Adverse Event Monitoring

Subjects will be monitored for SAEs at each study visit and telephone call. Serious adverse events will be reported on the SAE Form. If an adverse event has occurred, appropriate follow-up questions will be asked to determine the exact nature of the event. Appropriate medical records will be obtained, if needed. The study coordinator, in consultation with the site investigator, will determine if a reportable serious adverse event has occurred.

Active monitoring of SAEs will begin as soon as the subject signs the Consent Form and will continue until 30 days beyond the end of study participation for each subject. End of study participation is defined as the date the Study Termination Form is completed.

Serious adverse events should be followed to resolution or stabilization. SAE follow up documentation will occur using the SAE Follow-up form. In addition, documentation is needed in the patient’s source records, e.g., the electronic VA medical record and/or the subject’s study record.

Expedited Reporting of Serious Adverse Events:

All SAEs require prompt reporting within 72 hours of the site investigator becoming aware of the event. The SAE form will be promptly completed using the electronic data capture system approved for use in the study and documented in source records, e.g., the electronic VA medical record and/or the subject’s study record. The CSPCRPCC is responsible for evaluating all SAEs for patient safety concerns. The CSPCRPCC Study Pharmacist will collaborate with the Chairmen’s office during the review process as necessary.

Adverse events that are serious, related to the study interventions and/or associated medications, and unexpected will be reported to the site investigators and CRADO after review by the Study Pharmacist, Study Chairs, CSPCC Director, and CSPCRPCC Director.

XIII. STUDY ORGANIZATION AND ADMINISTRATION

The organization and administration of this cooperative study will include the following components: The Cooperative Studies Program Central Office in Washington, D.C.; the CSPCC at the Boston VA Health Care System, Boston, MA; the Study Chairman's Office at the VA Medical Center in Providence, RI; Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) at the Albuquerque VA Medical Center; Health Economics Resource Center (HERC), and the participating VA medical centers.

In addition, five committees will oversee the scientific and ethical conduct of the study – the CSSMRRB (formerly CSEC), the Study Group, the Executive Committee, the Data Monitoring Committee, and the Boston CSPCC Human Rights Committee. The Cooperative Studies Program Central Office in Washington, D.C. establishes overall policies and procedures that are applied to all VA cooperative studies through the Study
Chairman's Office, the Boston Coordinating Center, and the Albuquerque Pharmacy Coordinating Center.

The Study Chairman's Office and the Boston Coordinating Center jointly will perform the day-to-day scientific and administrative coordination of the study. This includes the development of the study protocol, preparation of the Manual of Procedures, and case report forms; ensuring that appropriate support for the participating centers is provided; scheduling of meetings and conference calls; answering questions about the protocol; conducting site visits; publication of newsletters; preparation of interim and final progress reports; and archiving of study data at the end of the study.

Interim statistical progress reports will be produced annually. Patient accrual and data quality will be monitored closely to ensure that the study is progressing satisfactorily.

The CSP Clinical Research Pharmacy Coordinating Center acts as a liaison in all VA cooperative studies between the study participants and the manufacturer of the study drug. This center will develop a drug information report and drug handling procedures, obtain and distribute the study medications; and provide advice and consultation about drug related matters during the course of the study.

The CSP Economics Coordinating Center (HERC) will work jointly with the Boston Coordinating Center to coordinate the collection of all of the data required for the economic analysis, and in conducting all interim and final economic analyses.

XIV. PUBLICATIONS

A. Publication Policy

It is the policy of the CSP that outcome data will not be revealed to the participating investigators until the data collection phase of the study is completed. This policy safeguards against possible biases affecting the data collection. The regular and ex-officio members of the DMC and the Boston CSPCC Human Rights Committee will be monitoring the outcome results to ensure that the study is stopped if a definitive answer is reached earlier than the scheduled end of the study.

All presentations and publications from this study will be done in accordance with the CSP policy as stated in the CSP Guidelines, March, 1996, p. 36.

The presentation or publication of any or all data collected by participating investigators on patients entered into the VA Cooperative Study is under the direct control of the study's Executive Committee. This policy is applicable whether the publication or presentation is concerned with the results of the principal undertaking or is associated with the study in some other way. No individual participating investigator has any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any or all of the data other than under the auspices and approval of the Executive Committee.
The Executive Committee has the authority to establish one or more publication committees, usually made up of subgroups of participating investigators and some members of the Executive Committee, for the purpose of producing manuscripts for presentation and publication. Any presentation or publications, when formulated by the Executive Committee or its authorized representatives, should be circulated to all participating investigators for their review, comments, and suggestions, at least four weeks prior to submission of the manuscript to the presenting or publication body. All publications must give proper recognition to the study’s funding source, including the Department of Veterans Affairs, and should list all investigators in the study. If an investigator’s major salary support and/or commitment is from the VA, it is obligatory for the investigator to list the VA as his/her primary institutional affiliation. Submission of manuscripts or abstracts must follow the usual VA policy. Ideally, a subtitle is used stating, "A VA Cooperative Study." A copy of the letter to the editor and the manuscript/abstract submitted for publication/presentation should be sent to the Chief Research & Development Officer, VA Headquarters, and, for information purposes, to the members of the study’s Data Monitoring Committee. The DVA contributions to the research project should be acknowledged in all written and oral presentations of the research results, including scientific articles, news releases, news conferences, public lectures, and media interviews.

All publications should state that it is a publication from a VA Cooperative Study. It should be accompanied by a copy of the letter of submission to the journal or publisher, and be reviewed and approved by the CSPCC Director prior to submission for publication.
XV. REFERENCES


34. Tanghetti EA. Comparison of 5-fluorouracil 5% and imiquimod 5% for actinic keratoses. *Cosmetic Dermatology.* 2004;17(11 S3):16-20.


2. Final Protocol V4.0
TABLE OF CONTENTS

EXECUTIVE SUMMARY ........................................................................................................... 2
I. BACKGROUND .................................................................................................................. 2
II. STUDY OBJECTIVES ....................................................................................................... 10
III. STUDY OUTCOME MEASURES .................................................................................... 11
IV. PATIENT POPULATION ................................................................................................. 13
V. INTERVENTIONS ............................................................................................................. 14
VI. ASSESSMENTS ............................................................................................................... 19
VII. ECONOMIC ANALYSIS ............................................................................................... 26
VIII. HUMAN SUBJECTS ........................................................................................................ 30
IX. QUALITY CONTROL PROCEDURES ........................................................................... 32
X. DATA MANAGEMENT AND DATA SECURITY ............................................................... 34
XI. BIOSTATISTICAL CONSIDERATIONS ......................................................................... 37
XII. GOOD CLINICAL PRACTICES .................................................................................... 43
XIII. STUDY ORGANIZATION AND ADMINISTRATION .................................................. 48
XIV. PUBLICATIONS ............................................................................................................ 49
XV. REFERENCES ............................................................................................................... 51

APPENDIX A: DEFINITIONS FOR CENTRAL HISTOPATHOLOGY
APPENDIX B: DNA BANKING
APPENDIX C: CONSENT FORM
APPENDIX D: BUDGET
APPENDIX E: CURRICULA VITAE
APPENDIX F: BIOSTATISTICAL AND RESEARCH DATA PROCESSING
APPENDIX G: RESEARCH DATA FORMS (CASE REPORT FORMS)
APPENDIX H: DRUG TREATMENT AND HANDLING PROCEDURES
APPENDIX I: DRUG INFORMATION
EXECUTIVE SUMMARY

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin, both of which are keratinocyte carcinomas (KCs), account for a half of all cancers in the United States, and over 100,000 diagnoses per year in the VA. The standard treatment for these KCs is excision of the lesion, and they cost the US health care system some $2.5 billion annually and about $100 million annually in the VA. There is no proven means to prevent KCs (except perhaps for a modest benefit of intensive daily sunscreen use). An effective prevention strategy would dramatically change the way high-risk patients are managed and could substantially reduce the costs of care. Our preliminary analysis indicates that the savings will be $116 per high-risk patient and will account for a total national savings of over $11 million. These findings imply that the study would pay for itself by the end of 4 years. We hypothesize that topical 5-fluorouracil (5-FU) chemoprevention will prevent skin cancer surgeries and will be cost-saving. To test this we propose a randomized controlled trial of 5-FU compared to a vehicle control to the face and ears in a high-risk population.

In the study, 1000 veterans at high-risk of skin cancer defined as at least 2 KCs in the prior 5 years, at least one of which was on the face or ears, will be randomized to 5-FU or a vehicle control cream, and followed for 2 to 4 years. The primary endpoint will be surgery for any KC on the face and ears. We will also assess the cost of care, quality of life, the side effects associated with treatment, and the prevalence and number of actinic keratoses, a skin cancer precursor and itself a cause of morbidity and cost. By targeting patients at high-risk, the study focuses on high-cost patients for whom this treatment could both improve outcomes (cancers and quality of life) and reduce costs.

I. BACKGROUND

A. Abbreviations

KC: keratinocyte carcinoma (basal cell carcinoma and squamous cell carcinoma of the skin)

BCC: basal cell carcinoma, a type of KC

SCC: squamous cell carcinoma, a type of KC

AK: actinic keratosis, a precursor of SCC

5-FU: 5-fluorouracil, widely used as a 5% cream for topical application. It also comes in other forms.

NMSC: nonmelanoma skin cancer, which includes keratinocyte carcinomas, merkel cell carcinoma, cutaneous lymphoma, dermatofibrosarcoma, and a variety of uncommon cutaneous malignancies.
BCCs and SCCs are keratinocyte carcinomas which share etiologic and clinical features. Both malignancies arise in the epithelium, histologically resemble keratinocytes, and are caused in large part by exposure to ultraviolet radiation from the sun or artificial sources. Both are diagnosed by biopsy. Both are believed to result from a defect in DNA repair after ultraviolet light damage. Both occur at very high frequency and multiplicity in patients with Xeroderma Pigmentosum, a rare heritable disease characterized by more than a 1000-fold increase in BCCs and SCCs and by a defect in repair of ultraviolet-induced DNA damage. These cancers are also more common with age and there is evidence that the DNA repair system in normal individuals becomes less efficient with aging.

While both BCC and SCC have sun exposure as their most important risk factor, they differ in other aspects. Iatrogenically immunosuppressed patients have very high risk of SCC, but not for BCC, and their SCCs are quite aggressive, whereas their BCCs are not. PUVA (psoralen plus ultraviolet A) phototherapy results in increases in SCC that are well-documented and many times larger than the relatively modest, poorly documented association with BCC. Even though BCC is about 3 times more common than SCC, SCC is responsible for more deaths because it is more likely to metastasize.

BCCs and SCCs and the major precursor of SCC, actinic keratosis (AK), occur most commonly on the face and ears. About 60% of SCCs arise from AKs, and an estimated 0.025% of AKs progress to SCC each year. Since a typical patient has many AKs, the risk of developing a SCC for the individual patient with AKs is about 1 to 2% per year. There are no common clinical precursors of BCC. The treatment for both BCC and SCC is generally surgical.

The diagnosis of AK is generally made on clinical grounds alone, without a biopsy. However, histopathologic evaluation is done when there is concern that the lesion may be a KC. In population-based studies, the clinical impression is confirmed in over 90% of subsequent biopsies, but this figure is less than 90% in individuals with existing KCs.

We propose to prevent surgeries for BCCs and SCCs by a cream applied to the face and ears, and thereby reduce the frequency of surgery for KCs on the face, and reduce morbidity from BCCs, SCCs, and precursor AKs. To determine its efficacy, we propose a randomized
trial of topical chemoprevention and its effect on skin cancer surgeries and cost, and occurrence of KCs and precursor lesions and quality of life.

1. KC is common and increasing in the US

KC is by far the most common cancer in the United States. Ten years ago an estimated one million cases were diagnosed per year in the United States. Since then the incidence has risen because of the aging of the population, the higher rates among the elderly, increased UV exposure from depletion of the ozone layer, and the rising popularity of indoor tanning in teenagers and young adults. Although the peak incidence of KCs is among the elderly, the long-term impact on younger adults permanently disfigured from facial KCs can be substantial. There has been a marked rise in the incidence of KC among young adults over the last 25 years, a 60% increase for BCC and over 300% increase for SCC. The rising incidence is likely to continue because more than three-quarters of one’s lifetime risk of KC is determined by exposures prior to the age of 18. Hence, potent preventive measures in this younger group, if adopted now, would not take effect until today’s young become old.

Veterans have a higher risk of KC now and in the future. Between 1999 and 2004, 777,768 KCs were diagnosed in 225,619 veterans. In FY03, there were 581,165 VA dermatology visits, of which 213,328 (37%) were for AKs. Veterans with service in areas of intense sun exposure, such as the South Pacific, Panama Canal Zone, Vietnam, Somalia, Lebanon, and the Persian Gulf have a greater risk of skin cancer.

2. KC causes significant morbidity and costs

Although KCs are usually cured, they cause considerable disfigurement and over a thousand deaths from KCs occur each year. KCs can cause local destruction of the nose, ear, and eyelid, producing deformity that leads to social isolation and rejection, facial paralysis (due to invasion of the facial nerve), visual impairment with loss of independence (when the orbit or eyelid is involved), breathing difficulties (from nasal deformity), hearing impairment compounded by inability to use conventional hearing aids (due to auricular deformity), chronic drooling (due to compromised function of the lip), ectropion and corneal erosions (from incomplete eyelid closure), and paraesthesias and sensory loss.

The economic analysis (Section VII) indicates that 5-FU treatment would save $116 per patient over 3 years. From 1999 to 2004 an average of 37,500 VA patients were diagnosed with a KC’s each year. At the end of three years, savings would accrue to $4,350,000.00 (37,500*116 = 4350000). To simplify, we round down to 4 million dollars as if we had saved $100 per patient for 40,000 patients. Then at the end of four years we will have saved a total of 11 million dollars: 4 million in year one, 4 million in year two, 2 million in year three, and 1 million in year four. After year two, we have discounted the subsequent cost benefit each year by 50%.
3. Prevalence and quality of life impact of AKs

AKs are estimated to cost Americans over $1 billion in direct and indirect costs. Of the 1131 veterans enrolled in the VATTC Trial (CSP #402, see section I.D), the number of AKs noted on their face and ears was a key correlate of worse quality of life on all three dimensions (i.e., symptoms, emotions, and functioning) independently of demographic factors or prior KCs.\(^{13}\)

4. Diagnosis and Treatment of KC

BCC and SCC are diagnosed by examination and biopsy. The most common treatment for KC is surgical excision. When they occur on the face and ears, Mohs surgery is often used to conserve tissue and to completely remove the malignancy. The surgeon excises thin sections of tissue around the entire periphery of the tumor, meticulously maps the sections, and has each section systematically examined microscopically, thereby searching the entire border of the excised tumor tissue for evidence of malignancy. Wherever residual tumor is found, more tissue is removed and examined in the same manner. The process ends only when clear margins are achieved. Although more expensive and time-consuming than other surgical approaches, Mohs surgery has the highest cure rates among all modalities for treating KC’s on the face and ears, and is superior to all other surgical techniques in tissue conservation.

Surgical approaches used to remove KC’s at other body sites are seldom used on the face and ears because they tend to alter the appearance or damage tissue adjacent to the tumor and raise the risk of significant deformity. These alternatives include electrodessication and curettage. Cryotherapy with liquid nitrogen spray is also sometimes used, although the healing time is longer and the resulting scarring unsightly. All of these can generally be performed under local anesthesia, although this may not be adequate for the most invasive tumors or those requiring extensive reconstruction.

There are other treatments including radiation therapy and a treatment involving a topical application followed by blue light phototherapy that is known as “photodynamic therapy”. These other treatments are not commonly employed in most settings because of poor efficacy, lower efficiency, greater morbidity, or the requirement for specialized equipment.

Non-surgical therapies are not commonly used for KC’s on the face and ears. In particular, radiation therapy carries a risk of inducing additional malignancies over time. Thus, it may be used in elderly patients who cannot tolerate surgery.

Two topical chemotherapeutic agents have been approved for treating some types of KC: 5-FU and imiquimod. 5-FU is indicated for superficial BCCs when conventional methods are impractical, and imiquimod is approved to treat superficial BCCs in immunocompetent adults with tumors less than 2 cm on the trunk, neck, or extremities. Neither is commonly used for tumors on the face and ears because conventional surgery has higher cure rates.
5. Treatment of AK

AKs are usually treated by destroying the lesion with liquid nitrogen. Cryotherapy is an office procedure that produces pain during the procedure, typically followed by erythema and blister formation. The resultant erosion or ulcer may heal with permanent residual hypopigmentation. The other common treatment is topical 5-FU cream and the most typical regimen is 5% 5-FU cream bid for 2 to 4 weeks. This treatment may produce erythema, discomfort, and erosions which can be minimized by stopping therapy before significant erosions and crusting develop, even if the targeted duration has not been achieved. The clinical observation is that inflammation is most severe in areas of severe actinic damage and generally heals with no residua. Topical imiquimod is also used, typically 2-3 times per week for 16 weeks. It may result in the same side-effects, and the course of the inflammation is similar to 5-FU.

In the VA in FY03, 101,092 visits for AK had a CPT code of 17000 indicating destruction, by cryosurgery in the vast majority of cases. 96,067 had more than one lesion treated in that visit with destruction. In that same year, 32,740 patients in the VA received prescriptions for topical medications for AKs. Of these, 87% received 5-FU. The other medications included imiquimod (4266 patients) and diclofenac (110 patients).

The cost to the VA in 2007 is represented in the table below:

<table>
<thead>
<tr>
<th>Drug Name:</th>
<th>Cost of Drug</th>
<th>Cost per Application</th>
<th>Cost per Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% 5-FU</td>
<td>$80.42 / 40gm</td>
<td>$2.01¹</td>
<td>$160.84³</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>$56.10 / 50gm</td>
<td>$2.24²</td>
<td>$280.50 – $448.80⁵</td>
</tr>
<tr>
<td>Imiquimod (12 packets of 0.25mg)</td>
<td>$92.55 / 3gm</td>
<td>$30.85³</td>
<td>$987.20⁶</td>
</tr>
</tbody>
</table>

¹ assumes a 1 gm application to cover face and ears
² assumes a 2 gm application based on package insert that indicates 0.5 gram covers 25 cm²
³ assumes 1 gm per application or 4 packets to cover face and ears
⁴ represents the cost for two 40 gm tubes - assumes BID for 4 weeks
⁵ assumes 2 gm application BID for 60 (5 tubes) to 90 days (8 tubes)
⁶ assumes 1 gm treatment 2X week for 16 weeks

6. Chemoprevention studies of KC may provide insights into the process of carcinogenesis

KCs are common, external and readily identified. Therapies may be externally delivered directly to large numbers of lesions or “pre-cancerous” regions. KCs are a human in vivo model with transformative oncogenic pathways similar to other malignancies. For example, the RB, p53, RAS, and PTCH pathways all appear to play significant roles in the development of skin cancers. Such pathway similarities have meaningful clinical
implications, such as the use of 5-FU for both colorectal cancer and cutaneous dysplastic lesions

Prior studies of retinoids have demonstrated that findings in cutaneous chemoprevention trials can directly contribute to treatment applications for other malignancies. In 1988, retinoids were shown to provide effective chemoprophylaxis against the development of KCs in patients with xeroderma pigmentosum. These findings provided significant conceptual support for chemoprophylaxis studies involving lung, breast, hepatocellular, bladder, and cervical carcinomas. Furthermore, later studies of retinoids have shown that they may inhibit the progression of pre-malignant conditions and decrease the frequency of secondary malignancies in upper aero-digestive tract malignancies. This illustrates the value of KCs as models because they are easily monitored and sampled and quite common.

C. Prevention

1. Background

Despite much effort devoted to prevention of skin cancers the incidence continues to climb. Many governmental and nongovernmental organizations in the United States and elsewhere, notably Australia, have developed costly and sophisticated long-term public health campaigns aimed at the prevention of skin cancers.

The primary cause of KCs and AKs is ultraviolet light exposure. Hence it is commonly recommended to avoid sun exposure, use sunscreens, and wear sun protective clothing. The increasing incidence of skin cancers (BCC, SCC, and melanoma) over the past several decades suggest that this advice has been ineffective. Sunburn rates are not decreasing among U.S. youth or among Australians, and exposure to ultraviolet radiation is increasing as a result of the popularity of tanning salons (a risk factor for KC).

The advice to avoid sun exposure conflicts with advice for other diseases. Recommended physical activity to prevent cancer and cardiovascular disease involves outdoor activities. Many health outcomes depend on adequate levels of vitamin D, typically acquired by ultraviolet B exposure, which also increases KC risk.

There are no trials of sun avoidance or protective clothing use for the prevention of any type of KC or AK. High SPF sunscreen use has been demonstrated in randomized trials to be effective in reducing AK incidence and multiplicity, and one trial has suggested an effect in the reduction of SCC incidence, although no effect was found on BCC risk. BCC is about 3 times more common than SCC overall. In the VATTC trial (see I.D), participants were at high risk (similar to this proposed trial), and BCC was twice as common as SCC. As mentioned above, efforts at sun protection have not translated into a population effect of reduced BCC or SCC incidence, and is unlikely to do so in the near future.

Successful chemoprevention of KC results from systemic retinoids in high doses, but not from low doses. Retinoid compounds have significant side-effects, sometimes even at low doses, so they are not used for chemoprevention outside of quite uncommon settings.
that are associated with extraordinarily high risk such as xeroderma pigmentosum or solid organ transplant recipients on chronic immunosuppressive therapy. In an effort to avoid side-effects, we evaluated a high-dose topical retinoid for chemoprevention in the VATTC trial (see section I D), and preliminary analysis suggested lack of efficacy.

2. Justification for chemoprevention treatment

There are no proven chemoprevention strategies for KC. Systemic retinoids are too toxic. It is common practice to treat actinic keratoses (AKs) to prevent SCC, but the efficacy of this practice, if any, is unknown.

Topical 5% 5-FU was chosen for this trial because it has been in widespread use since 1972 and is the most widely used of the medical treatments for actinic keratoses. It has a long record on which to base assessment of safety. It is the only topical medication approved for use for facial BCC whereas other medications and other commercially available concentrations of 5-FU (2%, 1%, and 0.5%) are not. It is less expensive than other medical treatments for AKs, including imiquimod, diclofenac, and photodynamic therapy.

5-FU is an analogue of uracil; the hydrogen at the C-5 position is replaced with fluorine. Intracellularly, 5-FU is converted into the active metabolites fluorodeoxyuridine monophosphate, fluorodeoxyuridine triphosphate and fluorouridine triphosphate. These active metabolites incorporate into RNA and DNA, as well as inhibit thymidylate synthase. 5-FU forms a stable complex with thymidylate synthase preventing the normal synthesis of dTMP necessary for DNA replication and repair. The downstream effects of thymidylate synthase inhibition and incorporation into RNA and DNA leading to inflammation and apoptosis are not well-understood.

It is common practice to treat AKs that are clinically apparent at the time of a visit to the dermatologist, whether or not they are symptomatic (bothersome) or have worrisome features. The most common treatment of AKs is cryotherapy (see I.C.2), which treats only one lesion, and does not have any effect on the remainder of the area (field) of skin. The second most common treatment in the VA is topical 5-fluourouracil cream (5-FU) applied to an area, not just to a particular lesion. The clinical impression is that when 5-FU is used to a field of sun-damaged skin, subclinical AKs become inflamed and resolve, as do the original, clinically recognized AKs.

Topical 5% 5-FU is also approved for treating superficial BCC, but lower concentrations are not. 5-FU is not commonly used for BCC treatment because it does not have as high a cure rate as surgical excision or electrodessication and curettage.

Only one trial has compared 5-FU and imiquimod; it found 5-FU superior to imiquimod for the treatment of AKs but we judged that trial to be of poor quality, and noted that it was sponsored by a manufacturer of 5-FU. A systematic review was published of therapy for AKs, but the quality of the source studies (as well as the review itself) was so poor and the heterogeneity so great, including pooling of 1% and 5% 5-FU treatments, that reasonable
conclusions cannot be reached. We note that the first author is an advisor and trialist for the manufacturer of imiquimod.

Imiquimod is approved for treatment of certain types of BCCs, but not for use on the face, unlike 5-FU. It is more expensive, less commonly used, and it comes in a form for which a vehicle control cream with similar appearance would be difficult to formulate. Diclofenac is generally thought to be less effective for AKs and is not commonly used. Photodynamic therapy is complex, requires considerable staff time and patient time to perform, and methods for its use vary (often requiring long incubation times and residual photosensitivity). It also requires specialized equipment which is only available at a few VAMCs.

AKs are common precursors of SCC, but only a small proportion of AKs progress (see I.B.3). As noted above, AKs are commonly treated (usually by liquid nitrogen cryotherapy, a rapid, outpatient procedure that affects only the AK) because of this risk of progression; although it is not known whether and to what degree such treatment is effective in reducing SCC risk (see I.C.2). Unlike cryotherapy of AKs, topical 5-FU can be used on the entire face and ears, and has the potential to eliminate precursors that are not clinically apparent as well as visible AKs. We hypothesize this will result in the most effective prevention of SCCs.

There is no clinically recognized precursor of BCC, although subclinical keratinocyte dysplasias may give rise to BCC. Topical 5-FU is particularly worth evaluating because it is effective in the treatment of superficial forms of BCC, and is approved for that indication. It may also effectively treat clinically unrecognized BCC precursors. It should be noted that topical 5-FU is not commonly used to treat clinically evident BCC despite FDA approval for that purpose, because it is not as effective as complete surgical excision, nor is the healing after treatment of fully evolved lesions as rapid as with surgery.

3. Impact on Prevention

If successful, this treatment could markedly reduce KC in the VA population. As the cost analysis details, the short-term reductions would precipitate larger reductions in long-term direct costs and future morbidity because unlike other chronic diseases such as diabetes, KC does not shorten life. It is unlikely that any institution outside the VA would conduct a clinical trial to establish that this relatively inexpensive treatment, available in generic form, leads to less surgery and fewer costly treatments. Prevention of recurrences can result in major cuts in the expense of treating this disease.

D. The VATTC Trial (Cooperative Studies Program Trial # 402)

The VA Topical Tretinoin Chemoprevention (VATTC) Trial (study chairman Martin A. Weinstock, MD, PhD) was a randomized trial of a retinoid cream, tretinoin 0.1% vs. the vehicle control cream, applied to the face and ears up to twice daily, to test the hypothesis that the tretinoin would reduce the incidence of BCC and SCC. 76% of participants had AKs on the face and ears, and 37% had more than 5 lesions on the face and ears. Our
analyses indicate that the intervention was not effective. The trial met or exceeded recruitment goals, the intervention was delivered appropriately, and follow-up was 97%. The trial demonstrated that intervention was ineffective because the chemoprevention agent itself does not reduce BCC or SCC incidence.

It should be noted that in the VATTC Trial, the preliminary evidence supporting the use of this agent was based primarily on oral administration of retinoid compounds, which is, however, impractical for large scale chemoprevention because of the of the side-effect profile (hence the trial of the high-dose topical agent). For the proposed VAKCC Trial, however, the preliminary evidence reviewed above is primarily based on use of the topical agent itself. Hence we can be more confident of the likelihood of successful chemoprevention.

The VATTC study demonstrates the feasibility of recruiting sufficient subjects for the current proposal. A total of 1131 veterans from six clinical centers completed the study and were followed for up to six years. All centers but one recruited enough patients (that site had a coordinator who fell ill, worked in her impaired state for some time, and ultimately succumbed to her illness). At one study site protocol violations in an unrelated study forced the site to halt all research studies. Poor performance led the VATTC study to drop one site. The replacement site then recruited over 200 patients who completed the study, exceeding study goals.

The VATTC study obtained 6341 biopsy specimens from 913 of the 1131 patients randomized. 3919 (99.8%) of the face/ears biopsy specimens were read by central dermatopathology as well as the local pathologist. 34 (3%) of participants withdrew.

II. STUDY OBJECTIVES

Primary Objectives:

To determine the effect of topical 5-FU treatment (compared to a vehicle control treatment) on reducing surgeries for KC on the face and ears. This is to be determined in high-risk patients in a 4 year trial (approximately 2 years recruitment; average follow-up 3 years). Everyone in the trial will receive enhanced patient education and free sunscreen for the duration of the trial.

Secondary Objectives:

To evaluate the cost-effectiveness of this intervention, and effect of the 5-FU treatment on the incidence of surgery for BCC, on the incidence of surgery for SCC, on cryotherapy to the face and ears and prevalence of AKs, on quality of life, and on the frequency and severity of specific side-effects of the treatment.
III. STUDY OUTCOME MEASURES

A. Primary Outcome

The primary outcome will be the time to diagnosis of the first KC on the face or ears for which surgery is performed. By requiring surgical treatment, we are focusing on the more consequential lesions associated with morbidity and cost for our primary outcome. It should be noted, however, that we expect approximately 91% of the KCs diagnosed in this study to be treated surgically (based on our VATTC Trial experience), as this is the standard treatment. This outcome uses a time-to-event survival analysis comparing the hazard rates with the two treatments. We considered other approaches including use of total number of events, but the time-to-event approach offers statistical advantages, and it makes maximal use of the follow-up experience, hence shortening the overall study time by allowing the last patients enrolled to have a shorter follow-up period than the first patients enrolled.

Since we are evaluating chemoprevention, the primary outcome is surgery for primary lesions, not recurrent lesions. Recurrent lesions are recognized by their occurrence in the scar from prior removal of the cancer. We understand that recurrent lesions occur when malignant cells remain after removal or destruction of a KC, and those cells are frequently deep in the skin and therefore less suitable for treatment with topically applied agents.

This endpoint will be ascertained either at the scheduled follow-up study examinations or at examinations requested by the patient. At each study visit, the participant will be questioned about any skin cancers or surgeries that may have occurred since their last visit. Potential KCs will be managed according to the standard of care. Any potential KCs designated for surgical intervention will be noted for later tracking on Form22: KC Treatment, and the VA electronic record will be reviewed to ascertain or confirm the occurrence of the KC and the surgical procedure. For all participants in the trial, all local pathology reports of biopsies from the skin of the face or ears will be read and diagnosed at the clinical site. Corresponding pathology reports will be reviewed at the chairman’s office over the course of the study to confirm the diagnosis of all lesions biopsied or otherwise surgically removed. The histopathologic specimens of surgically removed lesions will be reviewed independently by the central dermatopathologist for the purpose of this study (see IIIC1). If a surgically excised lesion has the diagnosis of KC on initial biopsy, subsequent re-excision or Mohs surgery layers slides will not be sent for central review, since the lesion already has a centrally reviewed diagnosis of KC and hence qualifies as an endpoint. Skin cancers diagnosed outside of the VA, and associated surgeries, will be systematically sought in all participants to insure that our outcome measure is complete. For any outside diagnosis or surgery, the medical record will be sought and reviewed. In the VATTC trial, 91% of KCs biopsied had a subsequent surgical treatment (some variety of excision or electrodesiccation and curettage), and diagnosis of KCs on the face and ears outside of the VA system represented only 1% of the total number of KCs on the face and ears during that 6-year trial.
We will use actual cancer occurrence for which surgery is performed, as opposed to occurrence of a precursor or intermediate marker, as the primary outcome because of the problems in the in reliability of diagnosis and counting precursor lesions\textsuperscript{36}, their variable natural history, which includes a high probability of apparently spontaneous resolution, and a small probability of progression to invasive cancer\textsuperscript{2,5}.

B. Secondary Outcomes

1. **Cost-effectiveness of the treatment strategy:** It is common for susceptible individuals to have multiple AKs and KCs. The cumulative resources devoted to their care and specifically the treatment costs are large (see I.B). The cost analysis will therefore look at potential short-term and long-term savings from this strategy in high-risk populations (see VII). KC treatments other than surgery, which are expected to be few, will also be included in this assessment.

2. **Time to occurrence of first BCC for which surgery is performed, and separately of first SCC for which surgery is performed:** The etiologic differences between BCC and SCC indicate that a chemopreventive intervention may have differential effects between the two histopathologic types of KC. As reviewed in Section I, there is substantial evidence that the proposed intervention will be effective for both histologic types. Since there are identifiable populations at greater risk for BCC, and others for SCC, delineating the value for each separately is worthwhile. We will also examine predictors of BCC and SCC occurrence.

3. **Number of BCCs, SCCs, and overall KCs requiring surgery per person-year of follow-up:** Because patients often will have multiple KCs, we will evaluate the number of BCCs, SCCs, and KCs per person-year of follow-up. This may show that the treatment reduces the overall numbers of KC over time.

4. **Time to occurrence of first KC, BCC, and SCC for which surgery is not performed.** This will allow us to determine any effect of the study intervention on a later decision to treat a skin cancer surgically, instead of by an alternative modality. The numbers not treated surgically are expected to be small (about 9\% of KCs diagnosed), so only an (unexpected) large effect could be noted in this analysis.

5. **Measures of AKs:** We will also measure AKs because the morbidity and cost associated with these skin lesions is large (see section I). Also, the intervention tested has known efficacy against AKs, so reduced AKs and reduced need for treatment of AKs may be important benefits of the regimen. We will count AKs greater than 5 mm in diameter, a reliable measure\textsuperscript{37}. We will also count and measure cryotherapeutic treatments as an outcome; this is the standard treatment for AKs. Cryotherapy treatments will be a component of the cost-effectiveness analysis. Any treatments for AKs other than cryotherapy will also be measured.
6. **Surgeries not for KC:** We will examine whether there is a difference between groups in surgery on the face and ears for lesions other than KC. This will also be a component of the overall cost-effectiveness analysis.

7. **Side-effects of treatment:** Specific indices of chemopreventive treatment side-effects (especially pain, itch, sores/crusts, and erythema) will be ascertained. The measurement will include questions regarding the presence and degree of symptoms such as pain/burning and pruritus of the face and ears as well as erythema.

8. **Quality of life:** Skin cancer can cause substantial anxiety, disfigurement, and other morbidity. For quality of life, we will use the Skindex (a published, validated, widely used quality of life instrument for skin disease)\(^3^8\). This is a brief questionnaire completed by the participant. We will also use the Skin Cancer Index (a published, validated quality of life instrument for patients with nonmelanoma skin cancer).\(^5^0-5^1\)

   Morbidity from KC may include both morbidity from the cancer and from the treatments. When cancer is diagnosed, treatment of AKs may result in short-term pain and long-term depigmentation that may be disfiguring. Hence the quality of life measures reflects morbidity due to the skin cancers, morbidity due to AKs, morbidity due to their treatment, and morbidity due to the chemoprevention interventions themselves.

9. **Exploratory analysis of endpoint location:** We will review photographs of endpoint lesions to ascertain any particular sub-areas on the face and ears at which the chemopreventive treatment may have been more or less effective.

10. **Nonsteroidal anti-inflammatory medications (NSAIDs):** We will assess use of NSAIDs (OTC and prescribed) to evaluate their relation to KC risk, since that association has been suggested but is controversial\(^4^5,4^6\).

### IV. PATIENT POPULATION

The study population will be selected for being at high risk for BCC and SCC. Each site will develop their own recruitment strategy consistent with VA policy. All participants will have a skin examination by a dermatologist and be found free of skin cancer at the time of randomization.

**Inclusion Criteria:** Two or more KCs in the prior 5 years and at least one of those occurred on the face or ears. The KCs do not count toward the inclusion criteria if they occur in an area of radiation therapy or on genital or perianal skin. Among the 1131 randomized in the VATTC Trial (see I.D), 976 (86%) had at least one facial/ear KC (that is by far the most common site for KC, see I.B.8), and therefore would meet these inclusion criteria. Among those 976, 47% developed at least one BCC endpoint (5-year life table probability 56%), and 25% developed at least one SCC endpoint (5-year life table probability 29%). The 5-
year probability of at least one KC was 69%. Insisting on a history of at least 1 KC on the face or ears will also mean that the patients are more likely to appreciate the rationale for chemoprevention, and will have increased motivation to comply with the treatment.

Exclusion Criteria:
1. Participants with KC at randomization.
2. Participants currently using or having used field therapy for AKs on the face or ears in the past 3 years. The vast majority of these field treatments would have been with 5-FU cream. We will allow recent use of therapies that are applied to individual AK lesions (e.g. cryotherapy), but not those that were used on an entire area (field) in the study treatment area.
3. Participants currently using or having used systemic 5-fluorouracil or oral capecitabine (Xeloda®) within the past 3 years.
4. Participants with known allergy to sunscreen, triamcinolone and/or 5-fluorouracil.

(Exclusions 5-10: We will exclude the small proportion who get their KCs for special reasons other than ultraviolet radiation exposure (see list below), since that etiologic difference, which is associated with a prognostic difference, could be associated with a biologic difference in response to chemoprevention efforts. These will include:
5. Solid organ transplant recipients, such as renal, hepatic, or cardiac transplant patients.
6. Individuals with genetic disorders associated with very high cancer risk such as
   A. basal cell nevus syndrome
   B. erythrodyplasia verruciformis
   C. xeroderma pigmentosum
7. Arsenic exposure
8. PUVA (Psoralen plus UVA) treatment
9. Cutaneous T-cell lymphoma
10. Prior or current radiation therapy to the face and/or ears

Additional exclusions (11-14) are:
11. Those who, in the opinion of the recruiting investigator, have very high mortality risk at randomization (less than 50% chance of surviving 4 years) due to comorbid illness such as metastatic cancer or COPD.
12. For women of childbearing potential an initial pregnancy test and ongoing birth control will be required for participation.
13. Patients with known dihydropyrimidine dehydrogenase (DPD) enzyme deficiency (they have increased toxicity from systemic 5-FU, although screening for this is not part of dermatologic practice and will not be part of this study)
14. Patients on methotrexate (these will constitute about 1% of potentially eligible individuals) because they may have more severe reactions to topical 5-FU.

V. INTERVENTIONS
A. Stratification and randomization

The participating center will submit the screening and baseline data electronically to the Project Manager at CSPCC for immediate confirmation of qualification and randomization. Randomization lists will be generated at the CSPCC based upon permuted random blocks of variable size to assure approximate balance over time and will be stratified by study site. Allocation will be approximately equal between groups. The MS InfoPath/SharePoint electronic data capture system that is being developed will allow the entire process to be completed during one patient visit. The treatment assignment and kit number will be assigned electronically using these two systems and will then be sent to the VA Pharmacy Coordinating Center in Albuquerque. Staff in Albuquerque will track the assignments and ensure that all centers are properly supplied with study drug.

The study chairman’s office at the Providence VAMC will liaison with the other centers and assume primary leadership responsibility for the trial. The Boston VA Cooperative Studies Program Coordinating Center (MAVERIC CSPCC) will manage randomization and serve as the primary statistical and data management coordinating center for the trial. The Albuquerque VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) will manage drug supply, accountability, and review of adverse event and serious adverse event data. Eligibility criteria will be gathered, confirmed, and stored in a central electronic file. Drug assignments based on randomization will be entered in the same file. Assignments of treatment will then be made via the internet for all sites.

B. Interventions

1. Both groups:

All participants will receive detailed patient education about skin cancer, including images of typical early skin cancer lesions, and will be counseled on sun protection and the use of sunscreen. Sunscreen will be provided to the participants free of cost for the duration of the trial. All participants will also be given detailed instructions on how to apply the medication, and shown photographs of patients with moderate to severe reactions to 5-FU to illustrate a possible reaction to the study medication. Participants will be counseled on when they should discontinue use of the study medication and contact the study nurse. Patients will not be paid for joining this study, but will receive $20.00 to $40.00 per study visit to help cover the cost of gas and other travel expenses.

2. Intervention group:

The intervention group will have topical 5-FU 5% cream applied twice daily for 4 weeks to the face and ears, to be initiated immediately after randomization. The FDA-approved treatment for AKs is twice daily for 2-4 weeks (28 to 56 total doses), and for superficial BCC is 3-6 weeks twice daily (42 to 84 total doses). These two schedules overlap; for this study the treatment duration will be 4 weeks (56 doses). The 5-FU will only be given once although multiple treatments might potentially be more effective. We expect to be able to
detect effectiveness of a single treatment. There are currently no data on which to determine the optimal interval between 5-FU chemopreventive treatments. We hypothesize that the 5-FU treatment will destroy KC precursors, and because of their slow progression will therefore have a prolonged effect on KC incidence, despite the short course of treatment. The ultimate use of this chemopreventive strategy will undoubtedly involve re-treatment. The data from this study will guide estimation of duration of effect of a single treatment and the appropriate length of a re-treatment interval (see XI.G.1.).

If the participant is unable to tolerate the twice daily 5-FU, they will discontinue the treatment and initiate “cool-down” treatment with triamcinolone 0.1% cream twice daily until the symptoms resolve. In these reactions, symptoms generally resolve within the first 3 days. Asymptomatic erythema typically resolves in about 2 weeks. At 3 weeks after stopping 5-FU, if and only if the participant has not received at least the minimum 2 week (28 dose) course, 5-FU treatment will be resumed on a once-daily basis to complete the 56 dose course. If this is not tolerated, the “cool-down” routine will be followed, but 5-FU will be stopped. It is commonly assumed that the inflammatory response indicates an adequate dose of the topical 5-FU has been received, in which case even those who stop early are likely to benefit from the chemopreventive effect of the experimental cream. Adverse reactions to the study medications and use of triamcinolone will be tracked by the study nurse and recorded on the form 23.

Clinical experience indicates the importance of counseling regarding possible reactions for the successful use of this agent. This counseling will be provided by the on-site study nurse, who will talk with all participants at each visit and bi-weekly by phone during the treatment. Study nurses will be trained for counseling prior to use and during use, and for appropriate handling of potential issues that may arise during and after treatment. Patients will be encouraged to call the study nurse with any questions that may arise during the study (see VB4). An additional unblinded dermatologist will be also be available to the participant at any time.

The placebo cream is a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl). The Efudex cream is 5% 5-Flourouracil in a vanishing cream base consisting of the same ingredients as the placebo. Based on these ingredients we do not expect study related adverse events due to use of the placebo cream other than the possibility of contact allergy or irritation.

3. Justification for focus on just face and ears:

There are four reasons for applying the chemoprevention treatment to just the face and ears in this trial. First, the face and ears represent just 3% of the body surface area, but 75% of KCs arise on these areas, so treating these areas is a cost-effective approach. In the VATTC Trial, which did not select for veterans with prior face/ear KCs (see section II.D), 3449 (68%) of the 5080 KCs among participants during the 5 years prior to enrollment and 65% of the KCs that occurred during the trial were on the face and ears.
Second, KCs of the face and ears are the most consequential in terms of potential for visible or functional deformity and for impairment of vital structures such as the eyes, ears, nose, facial nerve, and skull (see Section I A). The ear in particular gives rise to up to 47% of the ultimately fatal non-genital SCCs.\(^40\)

Third, the limited surface area of application is likely to enhance compliance. When 5-FU is applied for AKs, it is usually done by the patient to the face and/or ears which gives us confidence in its use for the chemopreventive purpose in a population that has already had multiple skin cancers. In the VATTC Trial, the chemopreventive agent also caused dermatitis and was applied to the face and ears once or twice daily, but in that trial it was applied for up to 6 years.

Lastly, our treatment strategy (see I.C.4) is most likely to be effective in these areas, since these are the areas in which 5-FU is most effective in treating AKs. When 5-FU is used in other areas, longer courses of treatment are needed to see an effect. Based on this experience, one presumes that it is also more effective for clinically inapparent incipient KCs on the face and ears than for similar lesions elsewhere on the skin. If that presumption is correct, it is another reason that testing the chemopreventive potential of this treatment strategy would be more powerful if tested on the face and ears than if tested elsewhere on the skin.

4. **Blinding:**

The control group will receive a physically identical cream that does not contain the 5-FU.

The trial is triple blinded. The study dermatologist and dermatopathologist will be blinded to treatment assignment, and will determine the primary endpoint of the trial. The endpoints will occur long after the 5-FU treatment is completed, and any resulting reaction has subsided. In the absence of any topical applications to the skin, skin cancers may or may not be accompanied by histopathologic signs of inflammation.

Neither the patient nor the blinded study dermatologist will be informed of the treatment group assignment. The blinded study dermatologist will not evaluate the participants between randomization and the first 6 month visit, in order to maintain the blind (see below). The side-effects of the cream will result in some unblinding of the patient that is substantial but not complete. In the VATTC Trial, which involved daily or twice daily application of tretinoin 0.1%, a cream which also frequently produces skin inflammation, we observed that the placebo control group frequently noted symptoms of inflammation on the skin. Although considerable inflammation may be expected in many but not all individuals in this proposed VAKCC trial, we expect there will be overlap in this symptomatology between the experimental and control groups.

To ensure adequate assessment, treatment and reporting of adverse events, up to four clinical staff may be associated with this trial at each local site: a primary investigator who will be blinded to which treatment the subject is receiving; a secondary investigator who will also be blinded to treatment and will be available to see patients when the primary investigator is
unavailable for study visits; a third dermatologist or dermatology nurse practitioner unblinded to treatment will be available during the treatment phase to clinically monitor the subjects, assess adverse events, and prescribe treatment for adverse events if necessary; and the study nurse.

Furthermore, all visits during the treatment phase will be with the study nurse, who may therefore become unblinded but who is not responsible for any of the study assessments that determine the primary outcome. Those are the responsibility of the study dermatologist, who will see the participant at randomization and at every six month visit, and the study dermatopathologist. The first 6 month visit will be long after any treatment-associated dermatitis or erythema has resolved. The participants will be instructed not to inform the study dermatologist about any reaction they may have had, and the study nurse will not inform the study dermatologist.

To assess the extent of unblinding, at the first regular (6 month) visit we will ask participants and dermatologists to guess whether they had received active treatment or placebo. Provisions will be made for unblinding if ever clinically required for the participants medical care, although this is unlikely.

5. Treatment of clinically diagnosed AKs:

Both groups will have cryotherapy treatments to individual spots on their skin as needed for clinically diagnosed AKs, as is the accepted standard clinical practice. “Spot” treatment to individual actinic keratoses with liquid nitrogen is by far the most common treatment of these lesions in the VA and nationwide (see I.C.2). It is not standard practice to biopsy AKs prior to treatment, and we will not require that here.

The key distinction here is between “spot” treatments, which will be allowed because they treat only the lesion and not an entire area of clinically nonlesional skin, and “field” treatments, which do treat an entire area, and will not be allowed (other than the experimental intervention). Spot treatments other than cryosurgery include curettage, electrodessication, or other surgical modalities, although these are not commonly used. A common feature of these spot treatments is that they are applied or performed by the clinician to the lesion only. Participants in both treatment groups will be allowed to receive these “spot” treatments as indicated, but will not be allowed to receive any of the “field” treatments unless the treating dermatologist concludes that other possible alternatives are unacceptable for this patient on medical grounds. Such instances will be quite rare, if they occur at all, and they will be recorded and reported to the study chairman’s office. Similarly, participants in both treatment groups will not receive any of the “field” treatments during the course of this study other than the experimental treatment immediately after randomization. Examples of other “field” treatments include diclofenac and photodynamic therapy with aminolevulinic acid and blue light, as well as 5-FU not in the usual 5% strength (e.g. 2%, 1%, and 0.5%). Unlike the other field treatments, photodynamic therapy must be applied by a clinician, and can be used with the medication applied only to the lesion, or to an entire area. The former would be a form of spot treatment, the latter a form of field treatment.
C. Dispensation of study medication

As part of this protocol, the Investigational Drug Information Record, (VA Form 10-9012) for both the Blinded 5% 5-FU (Efudex) and the Triamcinolone 0.1% will include the Local Site Investigator as an authorized prescriber. During the trial, if an unblinded practitioner is unavailable to prescribe the Triamcinolone 0.1%, it may become necessary for the blinded Investigator to prescribe. We expect this to be a rare occurrence and one that should only be utilized in emergent situations. If it is necessary for the Investigator to sign the prescription for Triamcinolone 0.1%, this must be documented as a protocol deviation via Case Report Form 25, Protocol Deviations, in the electronic Data Capture system (eDC). VA Central IRB Form 129- Report of Protocol Deviations or Violations, must also be submitted in accordance with VA Central IRB reporting guidelines.

VI. ASSESSMENTS

Patients will be assessed at baseline, at follow-up visits, and by telephone. We will also gather information from their medical records, and will conduct independent blinded central review of all biopsy specimens as part of this research trial.

Note that after randomization patients will return at six-month intervals for scheduled follow-up evaluations. They also may have unscheduled evaluations because of a lesion they have found between the regularly scheduled 6 month visits, although we expect this to be quite uncommon, if it occurs at all.

In addition to the semiannual follow-up visits, there will be follow-up visits with the study nurse at two weeks and four weeks after initiation of the chemoprevention medication or the corresponding control applications, and every two weeks thereafter if still on treatment. Finally, there will be follow-up by phone with the study nurse, and evaluation of medical records.

A. Baseline assessments

At baseline, all participants will have a full body skin examination by a study dermatologist, as is standard care but also to determine whether the potential participant meets criteria to be in the study. Any skin cancers on the face and/or ears will be removed prior to randomization. Participants will be eligible for participation in the study 30 days after completion of therapy for the skin cancer(s). For the purpose of this study actinic keratoses on the face and ears will be assessed as described in III.B.3. The dermatologist will also review medical records as needed (generally, the patient’s electronic VA record) to insure criteria are met for randomization, and to verify the complete count of skin cancers diagnosed in the prior 5 years with location and diagnosis of each. Copies of pathology reports of all skin cancers diagnosed in the past 5 years will be reviewed by the study chairman’s office to confirm consistent application of inclusion criteria and consistent counting and classification of prior cancers.

The study nurse will administer the baseline interview to capture key data on variables that will be used in later analyses including key predictors of BCC and SCC risk, such as prior
skin cancers, sun sensitivity, residential history, use of sun protection, NSAID use, family history of skin cancer, and smoking history. Past history of AK treatment will also be assessed, as well as the reaction to that treatment. Appropriate contact information for the participant and an alternate contact will also be ascertained at this time.

The MAVERIC analytic group has programmed a Charlson index that can be extracted directly from the SAS version of the Austin file. In addition, at baseline we will ascertain key predictors of mortality such as the items needed for the recently published mortality prognostic index \(^{41,42}\).

B. Assessment schedule

Baseline visit:
- Assess inclusion/exclusion criteria (10 mins)
- Review Informed Consent (15 mins)
- Randomization (5 mins)
- Perform complete skin examination (10 mins)
- Baseline Interview to obtain relevant history (30 mins)
- Quality of Life assessments (20 mins)
- Intervention overview (10 mins)
- Baseline photographs (10 mins)

Telephone interview by study nurse (10 min)
- Bi-weekly during intervention phase
- Once every three months during follow up

Brief follow-up visit at 2 and 4 weeks, and every two weeks thereafter if still on treatment
- Brief face/ears only assessment by study nurse (5 mins)
- Study nurse counseling and focused interview (15 mins)
- QOL assessments (20 mins) at 4 weeks
- Toxicity photographs (10 mins)

Follow up visits (every 6 months)
- Complete skin examination (10 min)
- Follow up interview (time since last visit) (15 min)
- If a potential skin cancer is to be biopsied, digital photograph to document precise location; if a surgery has been performed on a KC that had not been photographed, the location will be photodocumented (10 mins)
- QOL assessment at 12, 24, and 36 month visit (10 min)
- Photographs at first 6 month follow-up visit, and at some sites each 6 month visit after marking of AKs.
In order to better illustrate the typical assessment schedule for participants in VA CSP 562, the following tables have been included for review.

Table 1: Typical assessment schedule for a participant in VA CSP 562

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Timing of intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization</td>
<td>0</td>
</tr>
<tr>
<td>Telephone interview</td>
<td>Weeks 1, 3 and if still on treatment weeks 5, 7, 9, 11; Month 3, 9, 15, 21, 27, 33, 39, 45</td>
</tr>
<tr>
<td>Brief follow up visit</td>
<td>Weeks 2, 4 and if still on treatment weeks 6, 8, 10</td>
</tr>
<tr>
<td>Regular follow up visit</td>
<td>Month 6, 12, 18, 24, 30, 36, 42, 48</td>
</tr>
</tbody>
</table>

Sample Scenarios

Table 2: Assessment schedule for participant who undergoes a cool down period after initiating treatment for 1 week

<table>
<thead>
<tr>
<th>Date</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/3/09</td>
<td>Randomized into study</td>
</tr>
<tr>
<td>1/10/09 (week 1)</td>
<td>Patient stops study medication (14 doses complete); telephone contact; patient begins cool down period</td>
</tr>
<tr>
<td>1/17/09 (week 2)</td>
<td>Patient continues cool down period; brief follow up visit</td>
</tr>
<tr>
<td>1/24/09 (week 3)</td>
<td>Patient continues cool down period; telephone contact</td>
</tr>
<tr>
<td>1/31/09 (week 4)</td>
<td>Patient finishes cool down; study medication restarted at one dose per day; brief follow up visit</td>
</tr>
<tr>
<td>2/7/09 (week 5)</td>
<td>Therapy continues at once per day; telephone contact</td>
</tr>
<tr>
<td>2/14/09 (week 6)</td>
<td>Therapy continues at once per day; brief follow up visit</td>
</tr>
<tr>
<td>2/21/09 (week 7)</td>
<td>Therapy continues at once per day; telephone contact</td>
</tr>
<tr>
<td>Date</td>
<td>Activity</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2/28/09 (week 8)</td>
<td>Therapy continues at once per day; brief follow up visit</td>
</tr>
<tr>
<td>3/7/09 (week 9)</td>
<td>Therapy continues at once per day; telephone contact</td>
</tr>
<tr>
<td>3/14/09 (week 10)</td>
<td>Therapy complete (56 doses); brief follow up visit</td>
</tr>
<tr>
<td>6/3/09 (month 6)</td>
<td>Regular follow up visit</td>
</tr>
<tr>
<td>9/3/09 (month 9)</td>
<td>Telephone contact</td>
</tr>
<tr>
<td>12/3/09 (month 12)</td>
<td>Regular follow up visit</td>
</tr>
<tr>
<td>3/3/10 (month 15)</td>
<td>Telephone contact</td>
</tr>
<tr>
<td>6/3/10 (month 18)</td>
<td>Regular follow up visit</td>
</tr>
<tr>
<td>9/3/10 (month 21)</td>
<td>Telephone contact</td>
</tr>
<tr>
<td>12/3/10 (month 24)</td>
<td>Regular follow up visit</td>
</tr>
<tr>
<td>3/3/11 (month 27)</td>
<td>Telephone contact</td>
</tr>
<tr>
<td>6/3/11 (month 30)</td>
<td>Regular follow up visit</td>
</tr>
<tr>
<td>9/3/11 (month 33)</td>
<td>Telephone contact</td>
</tr>
<tr>
<td>12/3/11 (month 36)</td>
<td>Regular follow up visit</td>
</tr>
<tr>
<td>3/3/12 (month 39)</td>
<td>Telephone contact</td>
</tr>
<tr>
<td>6/3/12 (month 42)</td>
<td>Regular follow up visit</td>
</tr>
<tr>
<td>9/3/12 (month 45)</td>
<td>Telephone contact</td>
</tr>
<tr>
<td>12/3/12 (month 48)</td>
<td>Final regular follow up visit</td>
</tr>
</tbody>
</table>

Table 3: Assessment schedule for a participant in VA CSP 562 who undergoes a cool down period after initiating treatment for 2 weeks. As per protocol, the patient has received the minimal dose and treatment is not restarted.
C. Specific assessments

1. Lesion Diagnosis Determined by Central Pathology:

The primary outcome is BCC or SCC treated with surgery. For the purpose of this research the diagnosis of SCC and BCC will be defined (blind to treatment assignment) by assessment of the central pathologist because of (1) the critical importance of the primary outcomes, and (2) concerns about consistency of diagnoses across centers and (3) the variable experience and training of the pathologists in centers likely to be involved in this study. Many of these centers rely on pathologists who are not board certified in dermatopathology or who may have diagnostic criteria (for SCC in particular) that might be outside of the mainstream.

All skin biopsies will first be reviewed locally for diagnosis according to the standard of care for skin biopsies. All lesions on the face and ears will then be sent for central dermatopathologic review for study purposes. Standard dermatopathologic criteria (see Appendix A) will be used by our central dermatopathologist, and we will periodically reinforce use of these criteria and evaluate test-retest reliability (see below and section IX.A). The central dermatopathologist will not be aware of the local diagnosis for these lesions.

Our central pathology review for study purposes will be by a board-certified dermatopathologist who will read the same slides as those read locally. S/he is blinded to treatment group.

After initial review of a lesion by the local site pathologist, slides from all biopsies from the face or ears will be sent to the coordinating center for random distribution to the reference dermatopathologist. A barcode will be placed on the slide and its corresponding biopsy form 20 for tracking purposes. Slides will be packaged in slide boxes, bubble wrapped for mailing and sent in batches of 25 by Federal Express to the specified central dermatopathologist for review. After the review, the dermatopathologist will complete a Form 21 and return both the slides and the corresponding forms to the coordinating center by Federal Express. Slides will then be returned to the local VA where they originated. A 10% random sample of slides will be selected for independent blind rereading by the dermatopathologist 1 to 2 years later.

When there is disagreement between the central dermatopathologist and the original diagnosis, the treating clinician will be informed of the discrepancy so that he/she can...
appropriately care for the patient based upon the total clinical picture and his/her best medical judgment.

2. **Clinical (in-person) examination:**

After the baseline visit, there will be visits with only the study nurse at 2 and 4 weeks after initiation of treatment, and every 2 weeks thereafter until treatment is complete, to reinforce compliance, assess symptoms by self-report, and evaluate erythema and inflammation. These follow-up visits will be important for assessment of acute effects of the chemopreventive treatment and reinforcing counseling on proper use of medication. Besides the personal attention that this provides, this allows the primary investigator at the site to remain blinded to the treatment group. If at any time during the first six months a patient needs to see a dermatologist, one who is unblinded to the study will be made available to them. Participants will then be evaluated every 6 months by a blinded study dermatologist to assess skin lesions. At many VA sites dermatologists routinely take digital photos of lesions during patient visits to create more objective means of detecting new lesions and to assess changes in existing lesions. For the purpose of the study and with the patient’s consent, digital photographs will be used to document lesions as noted above. All patients who give permission will be photographed at baseline and at the 6 month follow-up, as well as during intervention. Photographs of any suspicious lesions that develop during the course of this study will also be taken. At some sites, photographs may be taken at all of the semiannual visits after marking actinic keratoses. A central photographic registry will be constructed by the MAVERIC CSPCC in a secure and encrypted manner. Photographs will be uploaded through the Sharepoint System and stored electronically within the study patients’ electronic record. If the local VAMC routinely takes photographs as part of dermatology visits, these photos will also be placed in the local patient medical record as standard practice for that VAMC. Patients will also be asked to consent to the use of these photographs in study related manuscripts and educational materials for healthcare providers. If they refuse to have their photographs used for these purposes or refuse to have photographs taken of their face and ears, they may still participate in the study.

3. **Telephone Contact:**

The study nurse at each site will speak with each participant once per week by telephone during the treatment if no visit is scheduled that week, and once every 3 months at other times if no study visit is scheduled that month (note that study visits are scheduled every 6 months, so this means one phone call between each pair of study visits). The purpose for the weekly calls is to enhance and monitor compliance with treatment and respond to any participant questions. These weekly phone calls during treatment will also be important for monitoring complications of the chemopreventive treatment and providing rapid feedback (at least weekly during the intervention phase) to study leadership and the data and safety monitoring committee regarding any complications, hence to allow changes to be initiated in a timely manner. The purpose of the every 3 month phone calls is to address any issues that may have arisen, assess any potential interval dermatologic or surgical care, and insure appropriate follow-up at 6 month intervals. This will enhance rapport between the
participant and the study nurse, and hence improve retention and adherence to study procedures.

4. **All contacts:**

At all patient visits and at all phone contacts during the first 6 months, participants will be asked to rate the following anticipated side-effects as none, mild, moderate, or severe, with specific reference to the face and ears: (a) redness; (b) itching; (c) burning; (d) soreness/tenderness; (e) crusting/erosions; (f) scaling/flaking; (g) swelling. In addition, at each of these contacts we will ask for the participant’s global assessment of the side effects of the treatment.

5. **Criteria for histopathologic evaluation:**

All lesions biopsied or excised will be submitted for local histopathologic diagnosis in accordance with usual procedures at the clinic, but then the slide will be sent to the data coordinating center for assignment to the reference dermatopathologist for evaluation, and that evaluation will include the diagnosis which will be used for study purposes. If the dermatopathologist has already diagnosed a slide from that lesion as KC, they will not be sent additional slides from that lesion (e.g. from a re-excision). We should note that any visible signs of 5-FU treatment (such as erythema or crusting) will have resolved before the first 6 month return visit. The ultimate diagnosis of BCC or SCC of surgically obtained tissue will be by the central reference dermatopathologist.

6. **Procedures for assessment of AKs:**

The study dermatologist examines each participant semiannually for the primary purpose of detection of any KCs that might be clinically apparent anywhere on the body. At that time they will also assess AKs on the face and ears by multiple methods. The primary method will be to count AKs greater than 5 mm in diameter. This is a method that has been demonstrated to be reliable.\(^{37}\) We will also assess by two other methods that are widely used or published for the purpose of determining their concordance with our primary method. The first of these is a simple count of all AKs regardless of size. The other is a procedure for assessing surface area covered by AKs as determined by the visual approximation technique that was described by Atkins et al.\(^{37}\) We will include AK assessment in our training/start-up meeting of investigators prior to the initiation of the trial and regularly over the course of the trial.

7. **Measurement of cream used:**

All tubes will be returned at the end of treatment to the study nurse. Study medication will be returned to the local pharmacy to allow for measurement of the amount of the intervention cream remaining, and thereby an estimate of amount used.

8. **Procedures for ascertainment of deaths:**
Deaths will be ascertained from the VA Vital Status File at the VA Austin Automation Center. This file allows for complete ascertainment as it pulls data from multiple sources, including: the BIRLS (Beneficiary Identification and Records Locator Subsystem) database, the DMF (Death Master File) from the Social Security Administration, and the National Patient Care Database. Deaths will also be noted by the study nurse at each site when they pull up the medical record to determine an appointment for a study visit for the participant that coincides with another visit to the VA medical center. If more information is needed on cause of death than is available in the VA medical record, a death certificate will be obtained.

9. **Procedure for Serious Adverse Event Monitoring:**

   If the subject is hospitalized at a non-VA institution, the subject will be asked permission in obtaining copies of medical records related to that hospitalization for purposes of SAE monitoring.

**VII. ECONOMIC ANALYSIS**

**A. Design Considerations for the Economic Analysis**

There are two components of the proposed economic analysis. First, we will conduct a cost-effectiveness analysis from both a VA and a societal perspective. Second, we will conduct a business impact, or cash-flow analysis from a VA perspective. The purpose of this second analysis will be to provide VA managers with the information that they need to accurately determine the financial impacts of adopting the study protocol as standard therapy. Both of these analyses are conditional on the main outcome of the study being an effective intervention. If the intervention doesn’t work, the economic analyses are moot, as the intervention will not be clinically adopted.

Skin cancer is a condition for which the treatment can be clearly separated from the treatment of other conditions. Thus, this study will not consider other health care costs; we will assume that the randomization equalizes these across the two study arms. The one exception to this is if a skin cancer metastasizes to another site. The costs and utilization associated with the treatment of metastatic cancers will be considered, conditional on site investigator verification that the metastatic cancer is related to BCC or SCC.

Preliminary calculations based on the effect sizes that the study is powered on project a cost savings associated with the intervention. Further, these cost savings will persist for a wide range of assumptions about the costs of therapy and the effectiveness of the intervention. Thus, there will only be conditional collection of health utilities information. If the initial analysis at the end of the trial shows that we need to value the relevant health state utilities, we will submit a supplemental proposal to CSSEC for the collection of health utilities. Study information from the skin cancer-specific quality of life measures collected during the
study, will be used to determine the health states that need to be valued. Community ratings will be obtained for these health states. Since study subjects are not required for this method of utility assignment, the collection of the utility data can be deferred without jeopardy to the proposed analysis.

B. Sources of Cost and Utilization Data

VA costs will be captured from the VA Decision Support System (DSS) National Data Extracts (NDEs). DSS is a comprehensive, activity-based hospital accounting system that VA uses to track its costs. Summary extracts are made from this system that track inpatient, outpatient, and pharmacy costs. These data are extracted and converted to SAS datasets at the VA Austin Automation Center (ACC) on an annual basis. They are usually available in February of each year.

Encounter data with ICD-9-CM codes for all encounters, and CPT codes for outpatient encounters are also available from the National Patient Data Base SE file at the ACC. These data will allow centralized tracking of all VA patient care encounters.

At many VA facilities at least some of the skin cancer-related care (especially Mohs surgery) is provided as contract care. To ensure complete data for this care, each site will be asked to identify the types of care that they routinely provide under contract or fee-basis care. Study forms will be used to capture the CPT codes for all fee-basis and contract care. While there are centralized databases of fee basis care, these data have never been carefully assessed for completeness. Further, starting in FY 2007, all fee-basis and contract care is supposed to be captured by DSS. Once the FY 2007 DSS extracts are available in early 2008, HERC will compare the data reported on the study forms with the fee-basis and contract care reported in DSS. If the DSS is found to accurately capture these data, use of the study forms for contract and fee-basis care will be discontinued.

C. Non-VA Health Care

Prior experience from CSP #402 found that 99% of the KC-related care was VA provided. Thus, while patients will be asked to self-report their use of related care obtained from a non-VA provider, the impact of errors of patient self-reporting will be minor. At enrollment, participants will be asked to bring copies of the billing statements for any non-VA skin cancer-related care to each subsequent follow-up visit. At each follow-up visit, the site coordinator will ask the patient if any non-VA skin cancer-related care was received since the last visit. If the patients does not provide copies of the billing statements, the site coordinator will use a study form to determine what non-VA care was provided. Fortunately, there are only a few types of patient care encounters that are relevant care. Thus, the study form will list each of the types of service. VA averages for these types of encounters will be used to assign costs to these encounter types. Patients will also be asked for the date of service. These self-reported uses of non-VA care will be cross-checked with the VA databases, especially the fee-basis files, to prevent double counting.
Patients will also be asked at enrollment if they are currently enrolled in Medicare (median age for CSP #402 was 71). If they are not currently enrolled in Medicare, they will be asked if they expect to enroll in Medicare during the study period. The consent form will include permission to access Medicare records. A finder file of all study patients will be submitted to VIREC, which is the VA repository of the Medicare data for users of VA care. These Medicare data will be used as a further check for study relevant non-VA health care utilization. Given the lag in the linking of the Medicare data to VA users, the Medicare data may not be available for the last year of the study at the time of analysis. But, the Medicare data will provide data for earlier years of follow-up and allow the assessment of the completeness of the patient self-report of use of non-VA care.

D. Assumptions for Preliminary Cost Analysis

The VA cost of 5-FU was obtained from the April 2007 list of current VA drug prices maintained by the VA Pharmacy Benefits Management (PBM) group. It was assumed that two 40g tubes of 5-FU would be sufficient for each course of chemo-preventive therapy. The April 2007 cost of a 40g tube of 5-FU was $80.42, yielding a per treatment cost of $160.84. The CPT codes were identified for Mohs facial surgery, and the 2005 VA frequency of use of these codes identify their relative use in VA. Using 2006 Medicare RVUs, conversion factors, and APC facility payment rates, we calculated an average cost of $830. This cost decreases to $715 if the surgery is done in conjunction with one of the more expensive types of reconstructive surgeries due to the facility payment methodologies for ambulatory surgery.

To estimate the VA costs for reconstructive procedures, we examine the “repair” codes recorded in VA encounters where Mohs surgery was performed. We used the weighted average of these payments, with adjustments for the Medicare facility payment methodology to obtain a weighted average VA cost for Mohs surgery and reconstruction of $1573.

Based on the information from CSP 402 and a search of centralized VA data, we know that the patients who will be enrolled in this trial have a high incidence of AK, which will almost always be treated with cryosurgery. Again, we used the actual VA use of CPT codes to calculate a weighted average cost for a cryosurgery of $138.

While it is possible that the intervention will reduce other VA costs of care, no other potential savings were included for this preliminary analysis. We acknowledge that there will probably be some added costs of the intervention for following up with patients by telephone during the intervention period. These will be captured during the actual analysis, with care to make sure that they exclude the additional visits/contacts that were part of the research project, not actual patient care. The cost of the initial visit at which the 5-FU is dispensed will not be included as this would be done at a regularly scheduled annual encounter for these high-risk patients.

From the power calculation of this trial, we are conservatively projecting an absolute reduction of 10% in the number of KC that will require surgical treatment. For the base analysis, we also assumed that on average, 0.75 cryotherapy treatments per patient would be
averted. This is a fairly conservative assumption, given that 5-FU is known to be an effective therapy for AK and the study patients average more than 1 AK per year, with an average follow-up of 3 years. These assumptions result in a net savings of $116.

We also tested the sensitivity of these assumptions. If no reductions in AK therapy are assumed, the net effect, due solely to the reduction in Mohs surgery, is a cost increase of $13. With the 0.75 cryotherapy treatments averted per patient for the treatment of AK, there are net savings as long as the reduction in the need for surgical treatment for facial KC is greater than 3.6%. Net savings also remain with 0.5 cryosurgeries averted per patient as long as the reduction in surgical treatment for facial KC is at least 5.8%.

E. Cost-Effectiveness Analysis

The cost-effectiveness analysis will be an intent-to-treat analysis, using an incremental cost-effectiveness ratio, and a societal perspective. All costs and benefits will be discounted at a 3% rate. We will monitor the development of the emerging concept of presenting the results in terms of a net health benefit, and will consider this method as an alternative for presenting the results. Essentially, we are acknowledging that this new method could change the consensus on how to report cost-effectiveness studies, and that we will be sensitive to this possibility.

Because this is a VA trial, the cost-effectiveness analysis will be repeated from a VA perspective. This will be done by revising the final analysis to only include the costs directly incurred by VA. This will have no affect on the QALY expressed benefit to the study subjects.

Given the strong prior that the study results will show the intervention to be effective and have a net cost savings (i.e. strong dominance), the utility/QALY assessment will be conditional. The changes in net health utilities associated with the different therapies in this study are likely to be relatively small. Standard indirect utility instruments such as the HUI and the EQ-5D are unlikely to be sensitive enough to detect these changes. The study will regularly collect data using disease-specific quality of life instruments. These instruments will provide sufficient information to allow the characterization of the health states that are most relevant to the study. If the initial analysis at study close-out shows that the net costs of the intervention may be positive, then supplemental funding will be requested to allow the outcomes from the disease-specific quality of life instruments to be mapped to utilities. These utilities will be assigned using a community sample of healthy adults. The study economist has prior experience with this method; he worked with colleagues at Stanford University to obtain community-rated utilities for the Activities of Daily Living scores that were used to measure patient functioning for Geriatric Evaluation and Management patients in CSP #006. Application of this method will allow utilities to be assigned to the disease-specific quality of life measures that will be recorded for study subjects at regular intervals. The advantage of this approach is that it avoids the significant expense of assigning utilities to health states unless it is necessary for the completion of the analysis. It is unlikely that this step will be required, given the preliminary analysis found cost savings at differences in
KC surgery rates down to differences that were so small that the intervention would not be considered more effective than current practice.

We also acknowledge the possibility that the interventions have differential effects on patient quality of life that could be the opposite of our expectations. The intervention will treat all patients to prevent the occurrence of KC in some patients (the intervention will also prevent the occurrence of AK in a larger fraction of patients). Thus, all of the intervention patients will experience some disutility associated with the treatment, while only a subset will receive the utility benefits of averted KC or AK. While the hypothesis is that the intervention arm will result in net higher disease-specific quality of life ratings, we will examine the results to confirm this. If the results of the disease-specific quality of life ratings don’t clearly show a net benefit to the intervention arm, this would also trigger the collection of utilities data from a community sample.

F. Cash-Flow Analysis

The VA is operated on a fixed global budget. VA managers must make decisions on where and how to allocate fixed resources. While traditional clinical trials results can make a compelling case about the effectiveness of an intervention, they don’t provide all of the information that managers need to implement the adoption of new technologies or treatments. Even if this study has the expected outcome of a net savings attributable to the intervention, this alone will not provide sufficient information for VA managers. This is because the study intervention requires an up front investment in chemo-preventive therapy. The up front costs will not be fully recouped in the first year. To allow VA managers to adequately plan for the adoption of chemo-preventive 5-FU therapy, we also plan to use the study data to calculate the expected cash flow affects of implementing the study intervention. We will use the actual utilization of care for patients in the control arm of the study to project when the averted treatments would have occurred, in terms of months since initiation of 5-FU treatment. These will be summarized on a quarterly basis, and compared with the cost of 5-FU therapy.

HERC has planned to include this type of cash-flow analysis in other CSP trials that are already in progress. The intent is to work with various VA leadership organizations to help disseminate this information. If this trials shows the intervention is effective, we will build on these previous management dissemination efforts. The purpose of this type of analysis is to make the results as useful as possible for VA managers. Feedback from this type of effort for other CSP trials will be incorporated into the exact dissemination plan.

VIII. HUMAN SUBJECTS

A. Consent Procedure

After a patient has been deemed eligible for the trial through screening and has demonstrated decisional capacity informed consent will be sought. Ultimately, the participating Site Investigator will obtain permission from the patient. The study coordinator at each site will introduce and explain the study to the patient and present
him/her with the detailed consent form and supplementary material to read and review. Subsequently, the participating investigator (or a designated physician) will review and discuss the study with the patient and answer any questions that the patient might have.

The general purpose of the study will be delineated. The treatment comparisons will be clearly described. The randomization process and a clear description of what is expected of the patient will also be described. The risks associated with treatments and procedures will also be addressed. The importance of patient confidentiality will be stressed describing the process for maintaining this confidentiality.

The patient will sign the informed consent in the presence of an independent witness not associated with the study. It must be ensured that the patient understands every aspect of the trial, including its risks and benefits, prior to signing the informed consent.

If the patient agrees, his/her consent to participate in the study will be recorded on the Agreement to Participate in Research form (VA form 10-1086 as modified by the VA Central IRB on June 4, 2008, see Appendix B). The original will be placed in the patient’s medical record. Copies of the signed consent form will be provided to the patient, the Research Office at the participating site (if required by the IRB), placed in the patient’s study file, and faxed and sent to the MAVERIC CSPCC in Boston at the time of enrollment in the study.

Informed consent requires that the patient understand the details of the study and agrees, without coercion, to participation in the study. To obtain informed consent, the following information shall be provided to each subject:

- Name of the study
- Name of the Principal Investigator
- Explanation that the study involves research
- Explanation of the purpose of the study
- Explanation of the treatment procedures
- Description of randomization.
- Description of the risks and benefits of participation in the study
- A description of alternatives to participation in the study
- Explanation that all records will be kept confidential, but that records may be examined by representatives of the VA and/or the FDA
- Whom to contact for questions about the research and about subjects’ rights.
- Whom to contact in the event of research-related injury.
- A statement that participation in the study is voluntary and that a decision not to participate or to withdraw from the study after initially agreeing involves no penalty, loss of benefits or reduction in access to medical care.
- A statement that the treatments provided as part of this study are free.

Merely obtaining signature consent from the patient does not constitute informed consent. However, the use of a standardized consent form aids in assuring that subjects receive adequate and consistent information about the trial and have consented to participate.
In conjunction with the informed consent procedure patients will review and be asked to sign the Authorization for Release of Protected Health Information From as required by HIPPA.

B. Surrogate Consent

No surrogate consent will be allowed.

C. Risks and Benefits

Any procedure has potential risks. The procedures used in this study may cause all, some or none of the risks and side effects listed. There is also the potential for rare or unknown risks occurring. Each study participant will be informed if any new information is developed during the study that might affect their willingness to continue to participate.

Study Cream Side Effects:
Common localized side effects of the study cream include a burning feeling and redness where the medicine is applied, increased sensitivity of the skin to sunlight, soreness or tenderness of the skin, itching, oozing, an open or crusted over ulceration or spot on the skin, a widespread skin rash in the area where the medicine is applied. The study cream may occasionally cause darkening of the skin or permanent scarring, although scarring is rare.

Triamcinolone “Cool Down” Cream Side Effects:
It is very unusual to have any side effects from the Triamcinolone cream, but it can rarely cause burning, itching, irritation, dryness, or a secondary infection.

Possible benefits of this study may include prevention of future skin cancers for patients who receive the active treatment. Information learned from this study may help us treat future patients who develop skin cancers.

IX. QUALITY CONTROL PROCEDURES

Standardization/Validation of Measurements

Each site will have two staff dermatologist investigators who will be responsible for all of the skin examinations. Prior to the initiation of the study, all investigators from the clinical sites will meet to review study procedures, including a training exercise to measure and maximize inter-rater reliability of clinical assessments. That session will involve patient volunteers and clinical images. Investigators will independently examine the faces and ears of the patients, note their clinical judgments on study parameters including presence or absence of a skin lesion worthy of biopsy as a potential KC, and including measures of AKs. Any differences in the results of these examinations will be discussed so that a consensus judgment can be reached and all investigators can re-examine the lesions with that consensus judgment in mind.
The study nurses will be trained to collect data for the study prior to and, most importantly at, the study kickoff meeting. They will be trained in the use of study medication and counseling regarding its use. They will be trained in standard responses to all anticipated side-effects of the study creams. They will be given the opportunity to review the protocol and case report forms prior to the meeting. At the meeting, study nurses will be given an opportunity to review source documents, and to practice administration of the study assessments and interview. Verbal feedback and discussion will follow to ensure that each nurse comprehends the proper methodology for assessment. The meeting will also cover an in-depth review of the study operations manual. Such a review will serve to reinforce the training described above and will orient the study personnel to the reference guides for the study.

The central dermatopathologist will quarterly review a selection of slides read in the prior 6 months that were not selected for the test-retest assessments.

Patient Management

For CSP 562, the site investigator at each site will be responsible for the management of his/her patients. If the patient misses a treatment visit or an assessment, the study nurse will contact the patient to reschedule the visit. Every effort will be made to accommodate the patient schedule and safety concerns.

Protocol Deviations

Documentation of any protocol breaches will be required. A Protocol Deviation form will be created by the MAVERIC CSPCC to ensure the proper tracking of events. Each protocol violation will be evaluated by the study chair, and a determination made regarding the validity of any justification for the violation. Any medical center or subject with repeated protocol violations in the absence of valid justification, and after remedial protocol training, will be recommended for termination to the Data Monitoring Committee (DMC). If any member of the DMC or the monitoring bodies for CSP 562 feel that adherence to the protocol will be detrimental to a participant’s health or well being, the interest of the participant will take precedence and the subject will be withdrawn after consultation with the executive committee.

Site Performance Monitoring

Strict adherence to the protocol will be monitored by the Data Monitoring Committee, the Executive Committee and the Study Group. By agreeing to participate in the study, the medical center delegates responsibility for global monitoring of the ongoing study to the Data Monitoring Committee, the Cooperative Studies Program Coordinating Center’s Human Rights Committee, the Cooperative Studies Scientific Evaluation Committee (CSSEC), the MAVERIC Cooperative Studies Program Coordinating Center (MAVERIC CSPCC) in Boston, the VA Central IRB and the Albuquerque Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC). However, the Research
Probation/Termination of Participating Centers

The recruitment rate and operational aspects of this study will be monitored continuously by the Study Chairman and CSPCC. Medical centers will only continue participation if adequate recruitment and proper procedures are maintained. Termination of a center will only be taken by the Executive Committee with the concurrence of the DMC and the Director, Cooperative Studies Program.

X. DATA MANAGEMENT AND DATA SECURITY

The MAVERIC CSPCC in Boston will manage the trial data for CSP #562 using a web-based Electronic Data Capture (EDC) system. The system allows site coordinators to enter patient data directly into a web based database and thus manage their patients, handle data clarifications, and correct patient data online. The data entered onto these forms goes directly into the study database. Parallel paper case report forms (CRFs) will be provided to site coordinators as guides for data collection. Patient questionnaires will use paper forms as a primary means of collecting data. These surveys will be faxed to the Boston CSPCC (MAVERIC) and will be entered directly into the database. This system is designed to make the process of patient data management easier, timelier, and more efficient. The software that will be used by the MAVERIC CSPCC utilizes MS InfoPath forms on a SharePoint platform. Accessing the system requires a VA intranet connection and a browser.

After the study is approved, the Study Chairman and Study Director will prepare an Operations Manual for site staff to guide them through the operation and management of the study and data collection tools. A training session will occur at the study kick-off meeting for all investigators and coordinators to assure uniformity in patient management, data collection, and study procedures. At training, coordinators will be provided with reference materials on the software tool and tasks. Once formal training is completed, user accounts utilizing a URL specific to the study to access and use the system and enter patient data will be activated. Accounts are password protected and are unique to the users’ functional study group (i.e. those for a site coordinator would differ from those of the coordinating center or site monitors). Formal training on the use of the InfoPath/SharePoint system for clinical study management will also be provided. Systems training will also be held at annual meetings, and on an as-needed basis for new study personnel.

For CSP 562, MS InfoPath/SharePoint designers will create a study-specific database that includes case report forms, visit schedule, and data queries. Data clarifications (DCFs) or data queries will be managed in two ways. Certain queries will be programmed into the forms that are designed to fire upon data entry. Additional DCFs will be programmed using other data analysis tools such as SAS and will be uploaded into the system for site coordinators to address. Furthermore the system will allow manual DCFs to be entered into the forms by the coordinating center as needed. Updates to the electronic forms and database can be generated during the study without impacting collected data. Study reports
can be generated from exported data in order to track the study progress and to monitor adverse events, in particular Serious Adverse Events. Study reports will be circulated to appropriate members, including the Principal Investigators, the Study Chairman, and the Data Monitoring Committee.

The goal of the MAVERIC CSPCC program is to develop a MS InfoPath/SharePoint electronic data capture tool that is fully compliant with US Federal regulations regarding electronic web based data capture systems established by the Food and Drug Administration under 21 CFR 11. Data entered directly into the database provides the official clinical record for data collection. Source documentation is handled in the same manner as a paper based system. All paper based records will be kept under lock and key. Electronic transmission of these records will occur via secure fax. The MS InfoPath/SharePoint electronic data capture system will be validated by the MAVERIC CSPCC Quality Assurance Team to ensure the integrity of the data capture software.

The servers housing the study databases will be located at a secure VA facility. This facility has yet to be determined but the one chosen will support round the clock web services and monitoring within a secure VA environment in order to provide an optimal infrastructure for the protection of sensitive information. The clinical database with all research data will be housed behind the VA firewall on VA owned and maintained servers. Accordingly, the information housed within the MS InfoPath/SharePoint system will be afforded the same level of security as all forms of VA protected and/or highly sensitive information. Additionally, the system will be monitored by the MAVERIC Quality Assurance and Information Technology teams to ensure that all applicable VA regulations and directives are strictly followed.

Backup copies of the database will be transferred behind the VA firewall to the MAVERIC CSPCC on a frequent basis depending on the study need (at least once per day). These backup copies will be transferred and stored across secure connections according to VA regulations and MAVERIC CSPCC operating procedures. Periodic off-site back-ups will be made as part of a comprehensive disaster recovery plan. The Director of Information Technology, will ensure that backup media are stored in compliance with all federal, and VA regulations on the storage of potentially sensitive information. The Director of Information Technology will also ensure that all backup media is encrypted in compliance with the current best practices established and approved by the Center Director(s). Encrypted backup media will be stored in a physically secure location with access restricted to essential personnel. Access to back-ups may be at the discretion of the Center Director(s) and/or the Director of Information Technology.

Access to the study data is heavily restricted to individuals with CSP approval to access the data. Individuals must be properly credentialed research staff and must be compliant with VA security trainings (i.e., Research Data Security, HIPAA and VA Privacy Training, Cyber-Security, and Good Clinical Practices). In addition, research data will be stored on VA secure servers with restricted permissions for copying and exporting data. Only properly approved Coordinating Center personnel will have the ability to copy and export data. These individuals have received training on the local SOP governing their permissions and will not
access or export data without written approval from the Coordinating Center Director. Furthermore, the permissions of the electronic systems are structured such that individual sites can only see the data for their study participants, and they cannot see or access the data for another clinical site or for another participant.

Access to PHI will be heavily restricted to individuals approved by CSP to have access to the data. Approximately 18 people in total will have access to some form of PHI for the study.

At the Clinical Sites a total of three people will have access to PHI. These individuals will be able to access all forms of PHI.
1. Principal Investigator
2. Co-Investigator
3. Nurse Coordinator

At the Coordinating Center a total of six people will have access to PHI. These individuals will be able to access all forms of PHI.
1. Project Manager
2. Data Manager
3. Biostatistical Staff (junior biostatistician and senior biostatistician)
4. Quality Assurance Officer
5. Project Director

At the Pharmacy Coordinating Center a total of six people will have access to PHI. These individuals will be able to access de-identified forms of PHI.
1. Clinical Monitors (3 in total)
2. Study Pharmacist
3. Adverse Event Specialist (Regulatory Affairs and Safety Officer)
4. Pharmacy Project Manager

Research data will only be stored on secure VA servers within the VA firewall. Data will not be stored on desktops or on University affiliate servers. Study data will be coded with a unique study identifier for each participant and stored in a de-identified manner. Identifiable information will be collected for patient tracking and safety purposes, but will only be kept for as long as the study is active. De-identified clinical data will be stored separately from the participant’s name, contact information, and real SSN. Access to the cross-walk file linking the participant’s identifiers and their study data will be restricted to the clinical site and to the project manager at the coordinating center. This file will be destroyed according to CSP policy.

When the study is on-going, the electronic data capture systems will utilize state-of-the-art technologies in order to protect the data during transmission. All of these technologies exceed the current VA standards for transport. In brief, electronic systems will employ secure socket layer technology and FIPS 140-2 compliant encryption algorithms to ensure that data is not vulnerable during transport. In addition, all data will be stored within the VA firewall and will be password protected at all times. Hard copy data will be sent via a
traceable mail system (i.e., FEDEX), via a courier, or via secure fax. Faxes are electronically routed to document management systems housed on VA protected servers located at the Regional Data Center in Philadelphia, PA. Access to these secure fax servers is restricted to the Coordinating Center personnel with approved access to the system. All secure fax servers are compliant with VA directive 1605.1 and 6500. All data security incidents will be reported in accordance with VA policy within one hour of discovering incident to:
1. The District (local) Information Security Officer (ISO)
2. The MAVERIC Data Security Officer
3. The Central IRB
4. the appropriate local IRB.

Quality control checks and clinical monitoring will enable the Coordinating Center to surveill the study database and the clinical sites to ensure that the data have not been improperly used or accessed. 21 CFR part 11 compliant audit trails and access logs will be checked routinely. In addition, the clinical monitors will provide continuing education on good clinical practices and will check all clinical site operations for violations of data security policies and best practices.

The clinical data for VA CSP 562 are considered property of the Cooperative Studies Program and shall not be sent off-site (i.e., outside of the VA) without expressed written permission from the CSPCC Center Director and CSP Central Office approval. All data transfer and data security policies of the VA, the Cooperative Studies Program, the MAVERIC CSPCC, and the local healthcare system will be closely followed. The MAVERIC Quality Assurance team will work closely with the local research compliance officer, the information security officer and the VA privacy officer as needed to ensure that data security and data transfers are handled appropriately.

Retention and destruction of data will be conducted according to CSP operating procedures and federal and local VA regulations. This will include data stored at the MAVERIC CSPCC and at the VA facility housing our servers. Identifiable data will be kept according to CSP policy as outlined in the “CSP Guidelines for the Planning and Conduct of Cooperative Studies.” Specifically, identifiers will be kept on site at the MAVERIC CSPCC for a minimum of five (5) years or as dictated by the FDA or other regulatory agency with specific written procedures (i.e., 2 years after last approval of a marketing application, etc). At the end of the record retention period, the CSPCC will conduct a review to determine if it is appropriate to archive the study data. If it is determined that the study data must be kept active, the CSPCC will retain the database in its entirety until the primary and secondary analyses are completed. At the completion of analyses, study data will be de-identified and stored indefinitely. If, however, the study is archived, the study data will be de-identified electronically and stored indefinitely.

XI. BIOSTATISTICAL CONSIDERATIONS

The study will enroll a total of 1000 patients, 500 of whom will receive the topical 5-FU-based treatment, and 500 of whom will receive the control treatment. We will enroll 500
patients per year for approximately two years to accrue 100 patients per site at 10 VA medical centers. The outcome measure distinguishes between surgical excisions of a pathologically confirmed KC lesion (either BCC or SCC lesion) and the rare excisions that result in any other diagnosis. Because chemoprevention may have no effect on other lesions, only KC lesions will be counted for the primary outcome. The primary outcome measure is:

The time after enrollment in the study until the first diagnosis leading to surgical treatment of a pathologically confirmed KC lesion.

In terms of the alternative hypothesis we wish to show that:

The 5-FU-based field treatment strategy is effective in the prevention of surgery for a pathologically confirmed KC lesion.

A. The Primary Outcome:

The null hypothesis is that the two treatment groups (5-FU intervention and control therapy) do not differ in their time-to-event hazard rates. The alternative hypothesis is that intervention has a lower hazard rate than control therapy with a hazard ratio for control therapy compared to intervention exceeding 1.42.

This four-year study will enroll patients for approximately 2 years so that the last patient enrolled will potentially have up to 2 years of follow-up. The first patient enrolled will potentially have up to 4 years of follow-up. On average, patients will potentially have approximately 3 years of follow-up. Thus, the power calculations are based on estimates of a surgically treated diagnosis of KC within 3 years.

Based on the VATTC study we expect the 3-year rate of diagnosis (but not surgical excision) of a pathologically confirmed KC lesion will be 49%. This follows from fitting a simple exponential curve to the rate of diagnosis, setting the 5-year incidence rate at 69%, and interpolating the 3-year incidence rate of 49% (see section IV: Inclusion criteria).

Instead of 49%, we have chosen a 3-year of 42% for the outcome, surgical excision of a pathologically confirmed KC lesion. We make this absolute reduction of 7% for several reasons. First, as noted in Section III.A, only 91% of diagnosed KC lesions were surgically excised in the VATTC study. This reduces the absolute rate by 5% from 49% to 44%. Second, a rare patient who developed both a SCC and a BCC at the same time will only be counted once. Third, in the proposed study, the 3-year incidence rate for KC may be slightly reduced because of differences between the old VATTC protocol and the proposed protocol. In the proposed trial physicians will adhere to their internal policies and tend to systematically remove many AK’s with cryotherapy and thereby may lower the 3-year KC rates. In the VATTC trial, centers were asked to take a watchful waiting policy on most AK’s, but tended to follow their own internal policies on this matter. Fourth, for the proposed trial we will exclude patients who had topical field therapy with 5-FU during the 3
years prior to enrollment, and we speculate that these patients may be at higher risk for KC’s than the eligible patients.

Under the null hypothesis:

The three-year KC surgery rate will be 42%

Under the alternative hypothesis for patients treated with 5-FU:

The three-year KC surgery rate will be 32%

The reductions attributed to treatment may be viewed in several ways. The absolute reduction from 42% to 32% is 10%, the relative reduction is \((42 - 32)/42 = 24\%\), and the hazard ratio (control hazard rate/treatment hazard rate) of 1.42 midway between the simple odds ratio, \(42(100-32)/(32(100 - 42)) = 1.54\) and the risk ratio \(42/32 = 1.31\).

B. Sample Size and Statistical Power Considerations

The results for the KC primary outcome measure, time until first SCC diagnosis, will be analyzed by means of the two-sided log-rank test to detect either a hazards ratio that exceeds 1.42 or is less than \(1/1.42 = 0.74\). The test will have a two-sided 4.8% type I error. (When added to the interim analysis that has a 0.2% Type I error, the overall type I error is 5%). The test has 90% power to detect a ratio of hazards of 1.42 or larger or 0.74 or less with a total of 1000 patients, 500 per study arm. This assumes that 8% of the patients either die or are lost to follow-up while on-study before a SCC diagnosis can be observed. The power for the log-rank test was computed using Schoenfeld’s formula\(^{48}\).

C. Interim Analysis

We will perform one interim analyses when the first 500 patients (250 in each study arm) enrolled have completed two years of follow-up. Assuming a uniform rate of enrollment over time this interim analysis should take place at the end of year 3. With an 8% loss-to-follow-up rate each study arm will have 210 evaluable patients.

The one interim analysis carried out when the 500th patient completes two years of follow-up has a small effect on overall type I error. The interim analysis has a Type I error of 0.2%. The interim analysis is two-sided, but the interim null hypothesis will only be rejected if the hazard ratio exceeds 2.39. If the hazard ratio is less than \(1/2.39 = 0.42\) then trial will be stopped for futility.

After 3 years the first patient entered will potentially have 3 years of follow-up and the last patient entered will potentially have 1 year of follow. Thus, the average potential follow-up will be two years. If we expect a 42% KC rate at three years then under the exponential model we would expect a 32% KC rate at two years.

Under the interim analysis null hypothesis:
The two-year KC rate will be 32% 

Under the interim alternative hypothesis for patients treated with 5-FU:

The two-year KC rate will be 16%

The reductions attributed to treatment may be viewed in several ways. The absolute reduction from 32\% to 16\% is 16\%, the relative reduction is \((32 - 16)/32 = 50\%\), and the hazard ratio (control hazard rate/treatment hazard rate) is 2.39.

We considered earlier times for interim analyses, but rejected this idea because sample sizes on the order of 150 per study arm only have modest power to detect very large effects.

For both the interim analysis and the primary analysis we considered the possibility that the effect of 5-FU merely delays the clinical emergence of a KC by a short period, such as 6 months. Then a wide gap between control and treatment arms, due to lower incidence in the treatment arm, might rapidly narrow with more follow-up. Indeed, this possibility led us to propose to monitor VA electronic records and passively follow patients after the four-year study ends to detect such narrowing. Finally, compared to other types of cancer KC’s are seldom fatal, so that the evaluation of costs to the VA and patient morbidity assume greater importance. We expect that to gather the data for these evaluations would prolong the trial past the early stopping date.

D. Censoring and Losses to Follow-up

We have made a conservative assumption about censoring of KC surgical events due to losses-to-follow. Overall, the VATCC study lost 20\% of the subjects, mostly due to death. The VATCC study had an average follow-up of up to 4 years whereas the proposed study has an average follow-up of up to 3 years. As in that trial, participants will continue to be followed through follow up visits and phone calls regardless of their use of study medication. Once enrolled in the trial reasonable effort will be made to retain the participant in the trial. Thus, we expect that 15\% = (3/4)*20\% of patients will die or be lost-to-follow-up during the proposed 4-year study. Furthermore, we assume that over one half of these deaths/lost-to-follow-ups (8\%), will occur before and 7\% will occur after a KC diagnosis.

In the VATCC study the average age at baseline was 71 years and many patients had serious comorbid conditions as gauged by the Charlson Index. We have accounted for this in item 9 in the exclusion criteria.

In the VATTC trial deaths tended to come later in the follow-up period. Because the proposed study is shorter than the VATCC study, death or lost-to-follow-up rates within two years of baseline should be lower than death or lost-to-follow-up rates between 2 and 4 years after baseline. Because KCs seldom cause death or losses to follow-up, we assume that when a patient dies or is lost-to-follow-up and thereby potentially censors a KC surgical event, the death or loss-to-follow-up is independent of both treatment assignment and disease.
E. Data Analysis Plan

The primary outcome hypothesis will be tested using a two-sided log-rank test to compare the hazard rate for one treatment group to that for another treatment group. A significant difference showing that the intervention strategy compared to the control decreases the hazard of surgery for pathologically confirmed KC will be regarded a positive result, whereas a result that shows intervention does not significantly differ from or, in fact, significantly increases the hazard rate will be regarded as a negative result. We will report the hazard rates, their ratio and the 95% confidence interval about the ratio. This will be followed by further refined analyses, using multiple linear Cox proportional hazards regression modeling, to take account of the effects of baseline covariates on the primary outcome measure. Covariates will include demographic and clinical factors (age, sex, smoking status, education, number of AK’s, history of BCC, of SCC, or both).

The regression modeling we shall employ will include a model with treatment by covariate terms to explore the possibilities of treatment by covariate effects (that is, exploration of potential subgroup effects). We will test the proportional hazards assumption by including a time-treatment interaction term in the model. We will use graphic methods to study goodness-of-fit.

F. Extended Follow-Up

The four-year study can be divided into two periods; namely, an approximate 2-year start-up and enrollment period, a 2-year follow-up period in which patients are only followed. Hence, the length of follow-up time may vary from 2-4 years. Assuming a uniform rate of enrollment the average potential follow-up time will be 3 years.

The power calculations account for both the varying amount of follow-up time and for the censoring of outcomes. Varying follow-up time and the length of the recruitment period have negligible effects on power. We have assumed an 8% rate of lost-to-follow-up combining the on-study death rate with the study lost-to-follow-up rate. Hence, the statistical power calculation is based on the 920 evaluable patients among the total of 1000 enrolled.

When the study ends after 4 years we will continue for one year to follow patients by tracking the medical procedures they have as reported in the VA Austin database. We will look for an excess of KC surgical events in the 5-FU treatment arm indicative of events delayed by treatment as opposed to prevented by treatment. We may also wish to contact participants after during this time if we become aware of some medical information related to the study that may benefit them.

G. Secondary Analyses
Secondary analyses are of several types; analyses directly related to the primary hypothesis of BCC and SCC surgical endpoints, quality of life as measured by the Skindex instrument, multiplicity of AK’s, and cost analyses. Cost analyses are described in section VII.

1. Time to surgery for a new BCC and for a new SCC:
In analyses directly related to the primary hypothesis, we will disaggregate KC into its components BCC and SCC. Then we will compare the treatments with respect to each of the two separate outcomes of the time to a diagnosis leading to surgery for a new SCC and time to a diagnosis leading to surgery for a new BCC using the analogous time-to-response analysis delineated for the primary analysis. For this secondary outcome each of the two parallel null hypotheses is that the two treatment groups (intervention and control therapy) do not differ in their time-to-event hazard rates. As in the primary analysis, we will begin with the two-sided log-rank test for each of the two outcome measures, time until the first BCC diagnosis leading to surgical treatment of a pathologically confirmed SCC lesion and time until the first BCC diagnosis leading to surgical treatment of a pathologically confirmed BCC lesion.

We will carry out additional time-to-event analyses of the aggregated KC outcome. We will apply the log-rank test to the data obtained from the extended follow-up beyond 4 years as in the primary analysis. This analysis will be done on both the final data set when the trial ends and on the extended follow-up data set. For each of these analyses we will report the hazard rates, their ratio and the 95% confidence interval about the ratio. This will be followed by further refined analyses, using multiple linear Cox proportional hazards regression modeling, to take account of the effects of baseline covariates on the primary outcome measure. Covariates will include demographic and clinical factors (age, sex, smoking status, education, number of AK’s, and history of BCC, of SCC, or both. The regression modeling we shall employ will include a model with treatment by covariate terms to explore the possibilities of treatment by covariate effects (that is, exploration of potential subgroup effects).

These secondary analyses are exploratory in nature and thus we have not assigned it a level of power. Extensive exploratory analyses will address the issue of the optimal time interval between applications of 5-FU therapy. Assuming that one 5-FU treatment reduces the hazard of surgical outcomes, we will separately study the disease endpoints of BCC, SCC, and KC to determine the shape of the hazard rate over time for the 5-FU treated and control patients. The objective will be to estimate the hazard rate for a new BCC, SCC, or KC in the treated and untreated groups. We will use an extension of the proportional hazards model, specifically with a Weibull frailty model that provides an explicit model for the hazard rate. In particular, we will test whether the hazard rate for patients treated with 5-FU remains lower than the rate for controls over time. A prolonged period of lower hazard rates would indicate the destruction of precursor lesions. Another pattern of interest would be an initial lowering of the 5-FU hazard rate that eventually rises to a higher level than the control hazard rate. This would indicate that 5-FU treatment delays the incidence of new KC’s. Assuming 5-FU is effective, the shape of the hazard function over time will guide us in constructing a schedule for when to re-administer 5-FU.
2. Quality of Life:
We will compare the treatments with respect to the change in the Skindex and Skin Cancer Index scores after one year and after two years. The change after one-year is the difference between the one-year score and the baseline score. The change after two years is the difference between the two-year score and the baseline score. Regarding these changes as continuous outcomes, we will use Student’s t-test to compare the treatments. Controlling for the covariates listed above we will carry out a linear regression analysis with treatment as the major factor. Confirmatory analysis will be done using combining the one-year, two-year, and three-year change scores into a repeated measures regression analysis. This analysis will treat the factor subject as a random effect and explore the possibility of different sizes of effect within each follow-up year.

3. Burden of Actinic Keratoses:
We will evaluate the effect of study treatment on the burden of actinic keratoses on the face and ears, as assessed by counts of large lesions, >= 5 mm in diameter. For the analyses of counts and for the number of spot treatments we will fix the follow period at two years and carry out a simple Poisson regression comparing the treatments and a more complex Poisson regression comparing the treatments and controlling for covariates. For the analyses of estimates of skin area affected (a continuous outcome) we will fix the follow period at two years and carry out a Student’s t-test comparing the treatments and a more complex linear regression comparing the treatments and controlling for covariates. To confirm this analysis we will collapse the Poisson counts into ordinal categories; none, 1-3, 4-10, 10 or more. We will rerun the analysis using polychotomous logistic regression. For each of the proposed analyses viewing baseline and each follow-up year as repeated measures we will also analyze the data with subject as a random effect using the SAS procedure NLMIXED.

4. Exploratory analysis of endpoint location:
We will review photographs of endpoint lesions to ascertain any particular sub-areas on the face and ears at which the chemopreventive treatment may have been more or less effective. We will partition the face and ears into sub-areas that have a reasonable number of endpoints. We will then compare groups stratified by sub-area in terms of survival analysis hazard rates using SAS Procedure TPHREG, and examine the variation of hazard rate ratio by sub-area.

5. Nonsteroidal anti-inflammatory medications (NSAIDs):
We will assess use of NSAIDs (OTC and prescribed) to evaluate their relation to the risk of KC since that association has been suggested but is controversial. This analysis will merely extend the proposed survival analyses by adding the covariate ‘NSAID use’.

XII. GOOD CLINICAL PRACTICES

A. Good Clinical Practices (GCP) and Site Review Program

The Site Monitoring, Auditing and Review Team (SMART) is responsible to assure that participating sites conduct the study in compliance with Good Clinical Practices. The SMART team will develop study specific tools for the sites and reviewers. The SMART
team will provide GCP training at the kick-off meeting and during subsequent on site visits. GCP reviewers will visit participating sites shortly after enrollment is initiated and annually thereafter to monitor investigator regulatory compliance, protocol adherence, and overall research practices. To promote GCP in the trial, SMART develops written GCP guidance and tools specifically for the trial and provides training in the use of these materials and in the principles of GCP. This training is an ongoing process that is initiated at the time of study kick-off and supplemented during on-site visits. Apart from regularly scheduled GCP review visits, an independent comprehensive GCP site audit may be conducted at any time at the request of study management or site reviewers.

In summary, SMART will accomplish the following:

1) Develop and provide sites with comprehensive study conduct tools including Essential Documents Binders, Patient Study Files, Source documentation requirements to aid in organizing and maintaining records in compliance with the protocol and GCP.
2) Present GCP training at the study kick-off meeting with reinforcement during periodic site review visits.
3) Develop study evaluation tools for site reviewers, including regulatory compliance, and verification of critical data points selected with the aid of the Study Chairman.
4) Conduct site GCP initiation visits to participating sites to aid in implementing the training, practices and tools provided CSPCC and SMART.
5) Conduct review visits to each participating site at least annually monitor investigator regulatory compliance, protocol adherence, and overall research practices.
6) Conduct a final review visit during the last year of study conduct to assure completion of all study tasks and appropriate archiving of study records.
7) Perform independent audits at sites as requested by CSPCC and other members of the study management and oversight teams.

Protection of the rights and welfare of patients is a primary concern of CSP. Informed consent will be documented in this trial by the use of a consent form prepared by each site investigator and approved by the local IRB; the consent form must be sent to the CSPCC before the trial may begin.

All patient data at sites will be stored in locked files. Computers with research subject data will be password protected to ensure confidentiality. The MAVERIC CSPCC is compliant with the Federal regulations regarding electronic web-based data entry systems established by the FDA under 21 CRF part 11.

Prior to the start of any study using DataLabs Clinical, extensive study specific validation will be performed. This process will be documented and placed on file at the MAVERIC CSPCC.

B. Summary of Monitoring and Auditing Plans

Monitoring Bodies
Monitoring the various aspects of the study will be carried out by: the Executive Committee, the Data Monitoring Committee (DMC), the Human Rights Committee, and the Study Group. These committees will meet according to the prevailing practice of the Cooperative Studies Program (at the beginning of intake, nine months later, and every twelve months thereafter). In addition, at the mid-point of the study, CSSEC will review the study.

The Executive Committee will oversee study operations, the performance of participating medical centers, and the quality of data collected. The members of the Executive Committee will be selected by the Study Chairperson from members of the Planning Committee and Participating Investigators. The Executive Committee formulates plans for publications and oversees the publication and presentation of all data from the study. Permission must be granted by the Executive Committee before data from the study may be used for presentation or publication.

The Data Monitoring Committee (DMC) will review the progress of the study and monitor participant intake, outcomes, complications, and other issues related to participant safety. They will also monitor the assumptions underlying sample size calculations for the study and alert the investigators if they see substantial departures as the data accumulate. The DMC will be composed of experts in dermatology and clinical trials. The Study Chairperson will make nominations to the Director, Cooperative Studies Program (CSP), who will make the final selection for the Board. The DMC will make recommendations to the Director of the Cooperative Studies Program as to whether the study should continue or be terminated. The DMC can consider participant safety or other circumstances as grounds for early termination, including either compelling internal or external evidence of treatment differences or feasibility of addressing the study hypotheses (e.g. poor participant intake, poor adherence). Data on study process will be provided to the DMC by the study biostatistician. The DMC will decide on specific intervals at which to meet. Every six months, the study biostatistician will provide the DMC with an interim summary report on the study status and on safety data for monitoring purposes.

The Human Rights Committee (HRC) at the Coordinating Center may review the study at the request of the Coordinating Center Director in order to provide suggestions regarding study participants protection. In addition, there may be HRC site visits to aid them in the determination that the participants’ rights and safety are being properly protected.

The Study Group, which consists of all participating investigators, will meet to discuss the progress of the study and any problems encountered during the conduct of the trial.

Clinical Monitors

The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that medications are properly stored and accounted for; verify that subjects consent for study participation has been properly obtained and documented; confirm that research subjects entered into the study meet inclusion and exclusion criteria; and assure that all essential documentation required by good clinical practices guidelines are appropriately filed.
Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and good clinical practices guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

The monitors will verify that study procedures are being conducted according to the protocol guidelines. At the end of the study they will conduct a close out visit to advise the storage of study records and return of unused study medication.

Monitoring Adverse Events and Serious Adverse Events

Timely and complete reporting of safety information assists study management in identifying any untoward medical occurrence, thereby allowing: 1) protection of safety of study patients, 2) a greater understanding of the overall safety profile of the study interventions and therapeutic modalities, 3) appropriate modification of the study protocol, 4) improvements in study design or procedures, and 5) compliance with regulatory requirements.

Role of the Local Site Investigator in Adverse Event Monitoring

The local site investigator will be responsible for the adverse event reporting requirements as outlined below:

a. Reviewing the accuracy and completeness of all adverse events (AEs) reported.

b. Compliance with local IRB policies for reporting AEs and/or serious adverse events (SAEs).

* NOTE: In November 2004, the VA published “Reporting of Adverse Events in Research to the Office of Research Oversight (ORO)” in VHA Handbook 1058.1. Investigators should be aware of this new reporting requirement. This requirement, however, does not eliminate the need for investigators to report both AEs and SAEs to the CSP#562 Sponsor as per the study protocol.

c. Reporting to the IRB safety issues reported by the Sponsor

d. Closely monitoring research subjects at each study assessment visit for any new AE and SAEs.

C. Collection of Safety Information

Adverse Events

Adverse events (AEs) are defined by the ICH for Clinical Safety Data Management (ICH-E2A) as “any untoward medical occurrence in a clinical investigation subject that is subjected to one of the study interventions that does not necessarily have to have a causal relationship with the interventions. An AE, therefore, can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study interventions.”
Adverse events collected in CSP 562 will be those related to the study intervention. Related events involve an assessment of the degree of causality (attribution) between the study intervention and the event. Site investigators will be asked to provide an assessment of relatedness. All adverse events with a reasonable causal relationship to the investigative treatment should be considered “related”. A definite relationship does not need to be established. For the purpose of CSP #562, the study interventions are topical use of 5-FU, and triamcinolone. The study interventions used in CSP #562 are standard treatment regimens currently used in usual clinical practice and have well-characterized adverse effect profiles.

During the study, data on adverse events will be collected spontaneously through patient reports, actively elicited at each clinic visit through open ended questionings and examination, and gathered at the time of telephone contact during the therapy period.

The collection of AE information will begin the day the subject signs the Consent Form and will continue until the end of study participation for each subject. Adverse events related to the study intervention that are reported to study personnel must be recorded on the Adverse Event Form and documented in source records, e.g., the electronic VA medical record and/or the subject’s study record. In this way, the site creates a permanent record that provides information on the subject’s clinical course while in the study.

Adverse events should be followed to resolution or stabilization. AE follow up should be documented in the patient’s source records, e.g., the electronic VA medical record and/or the subject’s study record. AEs should be reported as SAEs if they meet the SAE reporting requirements.

**Serious Adverse Events**

Serious adverse events (SAEs) are a subset of adverse events and are defined by the ICH for Clinical Safety Data Management and CSP Global SOP 3.6.1, as any untoward medical occurrence that:

a. Results in death
b. Is life threatening
c. Requires inpatient hospitalization or prolongation of existing hospitalization
d. Results in persistent or significant disability or incapacity
e. Is a congenital anomaly/birth defect
f. Any condition that, based upon medical judgment, may jeopardize the subject and require medical or surgical treatment to prevent one of the above outcomes

For CSP #562, all serious adverse events will be collected, including those considered related and unrelated to the study interventions. Study interventions are defined as are topical use of 5-FU, and triamcinolone. Serious adverse events with a reasonable causal relationship to the study interventions and associated medications should be reported as “related.” A definite causal relationship does not need to be established.
Serious Adverse Event Monitoring

Subjects will be monitored for SAEs at each study visit and telephone call. Serious adverse events will be reported on the SAE Form. If an adverse event has occurred, appropriate follow-up questions will be asked to determine the exact nature of the event. Appropriate medical records will be obtained, if needed. If the subject is hospitalized at a non-VA institution, the subject will be asked permission in obtaining copies of medical records related to that hospitalization for purposes of SAE monitoring.

The study coordinator, in consultation with the site investigator, will determine if a reportable serious adverse event has occurred.

Active monitoring of SAEs will begin as soon as the subject signs the Consent Form and will continue until 30 days beyond the end of study participation for each subject. End of study participation is defined as the date the Study Termination Form is completed.

Serious adverse events should be followed to resolution or stabilization. SAE follow up documentation will occur using the SAE Follow-up form. In addition, documentation is needed in the patient’s source records, e.g., the electronic VA medical record and/or the subject’s study record.

Expedited Reporting of Serious Adverse Events:

All SAEs require prompt reporting within 72 hours of the site investigator becoming aware of the event. The SAE form will be promptly completed using the electronic data capture system approved for use in the study and documented in source records, e.g., the electronic VA medical record and/or the subject’s study record. The CSPCRPCC is responsible for evaluating all SAEs for patient safety concerns. The CSPCRPCC Study Pharmacist will collaborate with the Chairmen’s office during the review process as necessary.

Adverse events that are serious, related to the study interventions and/or associated medications, and unexpected will be reported to the site investigators and CRADO after review by the Study Pharmacist, Study Chairs, CSPCC Director, and CSPCRPCC Director.

XIII. STUDY ORGANIZATION AND ADMINISTRATION

The organization and administration of this cooperative study will include the following components: The Cooperative Studies Program Central Office in Washington, D.C.; the CSPCC at the Boston VA Health Care System, Boston, MA; the Study Chairman’s Office at the VA Medical Center in Providence, RI; Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) at the Albuquerque VA Medical Center; Health Economics Resource Center (HERC), and the participating VA medical centers.
In addition, five committees will oversee the scientific and ethical conduct of the study – the CSSEC, the Study Group, the Executive Committee, the Data Monitoring Committee, and the Boston CSPCC Human Rights Committee. The Cooperative Studies Program Central Office in Washington, D.C. establishes overall policies and procedures that are applied to all VA cooperative studies through the Study Chairman's Office, the Boston Coordinating Center, and the Albuquerque Pharmacy Coordinating Center.

The Study Chairman's Office and the Boston Coordinating Center jointly will perform the day-to-day scientific and administrative coordination of the study. This includes the development of the study protocol, preparation of the Manual of Procedures, and case report forms; ensuring that appropriate support for the participating centers is provided; scheduling of meetings and conference calls; answering questions about the protocol; conducting site visits; publication of newsletters; preparation of interim and final progress reports; and archiving of study data at the end of the study.

Interim statistical progress reports will be produced annually. Patient accrual and data quality will be monitored closely to ensure that the study is progressing satisfactorily.

The CSP Clinical Research Pharmacy Coordinating Center acts as a liaison in all VA cooperative studies between the study participants and the manufacturer of the study drug. This center will develop a drug information report and drug handling procedures, obtain and distribute the study medications; and provide advice and consultation about drug related matters during the course of the study.

The CSP Economics Coordinating Center (HERC) will work jointly with the Boston Coordinating Center to coordinate the collection of all of the data required for the economic analysis, and in conducting all interim and final economic analyses.

XIV. PUBLICATIONS

A. Publication Policy

It is the policy of the CSP that outcome data will not be revealed to the participating investigators until the data collection phase of the study is completed. This policy safeguards against possible biases affecting the data collection. The regular and ex-officio members of the DMC and the Boston CSPCC Human Rights Committee will be monitoring the outcome results to ensure that the study is stopped if a definitive answer is reached earlier than the scheduled end of the study.

All presentations and publications from this study will be done in accordance with the CSP policy as stated in the CSP Guidelines, March, 1996, p. 36.

The presentation or publication of any or all data collected by participating investigators on patients entered into the VA Cooperative Study is under the direct control of the study's Executive Committee. This policy is applicable whether the publication or presentation is
concerned with the results of the principal undertaking or is associated with the study in some other way. No individual participating investigator has any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any or all of the data other than under the auspices and approval of the Executive Committee.

The Executive Committee has the authority to establish one or more publication committees, usually made up of subgroups of participating investigators and some members of the Executive Committee, for the purpose of producing manuscripts for presentation and publication. Any presentation or publications, when formulated by the Executive Committee or its authorized representatives, should be circulated to all participating investigators for their review, comments, and suggestions, at least four weeks prior to submission of the manuscript to the presenting or publication body. All publications must give proper recognition to the study’s funding source, including the Department of Veterans Affairs, and should list all investigators in the study. If an investigator's major salary support and/or commitment is from the VA, it is obligatory for the investigator to list the VA as his/her primary institutional affiliation. Submission of manuscripts or abstracts must follow the usual VA policy. Ideally, a subtitle is used stating, "A VA Cooperative Study." A copy of the letter to the editor and the manuscript/abstract submitted for publication/presentation should be sent to the Chief Research & Development Officer, VA Headquarters, and, for information purposes, to the members of the study's Data Monitoring Committee. The DVA contributions to the research project should be acknowledged in all written and oral presentations of the research results, including scientific articles, news releases, news conferences, public lectures, and media interviews.

All publications should state that it is a publication from a VA Cooperative Study. It should be accompanied by a copy of the letter of submission to the journal or publisher, and be reviewed and approved by the CSPCC Director prior to submission for publication.
XV. REFERENCES


CSP 562 VA Keratinocyte Carcinoma Chemoprevention Trial  Protocol v 4.0  02/12/2016Page 55 of 55
1. EXECUTIVE SUMMARY

Due to complications with the VA contracting process for our three study dermatopathologists, we were unable to use the joint evaluation of all three as our primary diagnosis for CSP562. We ultimately discovered, however, that we could obtain the diagnosis of one of the three, Dr. Robinson-Bostom, for all potential endpoints because of her pre-existing agreements with the VA. We determined that the agreement between her diagnosis and the evaluation of all three for the first 185 biopsies was near perfect agreement, much better than the agreement of the three with the local pathology reading. Hence we seek to substitute Dr. Robinson-Bostom's diagnosis for the evaluation of the three dermatopathologists originally proposed for the purpose of determining endpoints for CSP562.

2. THE PROPOSED STUDY PROTOCOL AMENDMENT/ SUBPROTOCOL WAS APPROVED BY:

☐ Human Rights Committee  ❑ Data Monitoring Committee

❑ Study Executive Committee

3. IMPACT OF THE PROPOSED STUDY PROTOCOL AMENDMENT/SUBPROTOCOL ON THE COORDINATING CENTER(S) AND STUDY:

a) Workload – Increased workload and additional time for single dermatopathologist to perform slide adjudication

b) Budget – No Impact

c) Participating Centers – Delay in return of pathology slides to sites

d) Duration of the Study – The active study phase concluded as planned. However, due to the contracting issues and the additional time required for all of the slides to be read by a single dermatopathologist, there has been a delay in analysis of the study data and preparation of the final results manuscript and subsequent publication.
e) Recruitment - no change

f) Results and Conclusions of the Study - This will have no impact on the study results.
3. Summary of changes to the protocol
Updates to the Protocol

On occasion, changes will be made to the study protocol. It is vital that these changes are reflected in your copy of the protocol. The following serves as a permanent record of all changes and additions that have occurred since the initial printing. A new version of this page will be updated and emailed to each center every time one or more pages in the protocol are modified. Please be sure to replace the old version of this page with the new version at the same time you replace the old version of the protocol. Also, be sure to update all copies of the protocol located at your center to reflect the newest version number. A printed copy of the new version of the protocol must be added to the Protocol & Amendments section of the Essential Documents Binder. The protocol log must also be updated to reflect the new version number and date of issue.

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<td>June 25, 2010</td>
<td>Version 1.0</td>
<td>Version 1.1</td>
<td>References to “CSSMRB” and “Cooperative Studies Scientific Merit Review” were changed to “CSSEC” and “Cooperative Studies Scientific Evaluation Committee” respectively.</td>
<td>Updated to reflect current terminology</td>
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<td></td>
<td>26, 33, 44, 48</td>
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<td>Section C. Specific Assessments, was modified to add “Section 9. Procedure for Serious Adverse Event Monitoring. If the subject is hospitalized at a non-VA institution, the subject will be asked permission in obtaining copies of medical records related to that hospitalization for purposes of SAE monitoring.”</td>
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<td>Revise the section the Human Rights Committee (HRC) from meeting every 12 months to review the study to reviewing “at the request of the Coordinating Center Director.”. Language regarding</td>
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<td><strong>July 1, 2011</strong></td>
<td>Version 1.1</td>
<td>Version 2.0</td>
<td></td>
<td>Administrative approval from Central Office for 3 month no cost enrollment extension until next CSSEC meeting Word changed to reflect that length of recruitment phase of protocol is <strong>not exactly 2 years, but approximately 2 years.</strong></td>
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<td>10, 37, 38</td>
<td>10, 37, 38</td>
<td>“Approximately” added in front of phrase “2 years”</td>
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<td><strong>December 16, 2010</strong></td>
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<td>References to “CSSMRB” and “Cooperative Studies Scientific Merit Review” were changed to “CSSEC” and “Cooperative Studies Scientific Evaluation Committee” respectively.</td>
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<td>January 20, 2012</td>
<td>Version 2.0</td>
<td>Version 3.0</td>
<td>Section V. Interventions, was modified to include:</td>
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<td>“Section C. Dispensation of study medication:</td>
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<td>As part of this protocol, the Investigational Drug Information Record,</td>
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<td>(VA Form 10-9012) for both the Blinded 5% 5-FU (Efudex) and the Triamcinolone 0.1% will include the Local Site Investigator as an authorized prescriber. During the trial, if an unblinded practitioner is unavailable to prescribe the Triamcinolone 0.1%, it may become necessary for the blinded Investigator to prescribe. We expect this to be a rare occurrence and one that should only be utilized in emergent situations. If it is</td>
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<td>In response to the VA Central IRB request, the Study Protocol has been revised to clarify dispensation of the study medication for this trial.</td>
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necessary for the Investigator to sign the prescription for Triamcinolone 0.1%, this must be documented as a protocol deviation via Case Report Form 25, Protocol Deviations, in the electronic Data Capture system (eDC). VA Central IRB Form 129- Report of Protocol Deviations or Violations, must also be submitted in accordance with VA Central IRB reporting guidelines.

<table>
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<tr>
<th>Date</th>
<th>Version 1.1</th>
<th>Version 2.0</th>
<th>Notes</th>
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<tr>
<td>July 1, 2011</td>
<td>Version 1.1</td>
<td>Version 2.0</td>
<td>Administrative approval from Central Office for 3 month no cost enrollment extension until next CSSEC meeting. Wording changed to reflect that length of recruitment phase of protocol is <em>not exactly</em> 2 years, but approximately 2 years.</td>
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<td>10, 37, 38</td>
<td>10, 37, 38</td>
<td>“Approximately” added in front of phrase “2 years”</td>
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<tr>
<td>December 16, 2010</td>
<td>Version 1.0</td>
<td>Version 1.1</td>
<td>References to “CSSMRB” and “Cooperative Studies Scientific Merit Review” were changed to “CSSEC” and “Cooperative Studies Scientific Evaluation Committee” respectively. Updated to reflect current terminology</td>
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<td>26, 33, 44,48</td>
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<td>26</td>
<td>Section C. Specific Assessments, was modified to add “Section 9. Procedure for Serious Adverse Event Monitoring. If the subject is hospitalized at a non-VA institution, the subject will be asked permission in obtaining copies of medical records related to that hospitalization for purposes of SAE monitoring.” ICF language mandated by the VA CIRB</td>
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<td>Revise the section the Human Rights Reflects new functionality of Human Rights Committee.</td>
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<td>Committee (HRC) from meeting every 12 months to review the study to reviewing</td>
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<td>at the request of the Coordinating Center Director. Language regarding attendance of HRC members at DMC meetings and the reports they will be presented have been removed.</td>
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CSP 562: The VA Keratinocyte Carcinoma Chemoprevention Trial

Updates to the Protocol

<table>
<thead>
<tr>
<th>Revision Date</th>
<th>Old pages</th>
<th>New pages</th>
<th>Subject</th>
<th>Justification</th>
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<tbody>
<tr>
<td>2/5/2016</td>
<td>V3.0</td>
<td>V4.0</td>
<td>Change from ‘a panel of 3 board-certified dermatopathologists’ to ‘a board-certified dermatopathologist.’ Deletion of ‘A lesion will be considered a KC if at least 2 of the panel members diagnose it as a KC. The dermatopathologists will review a training set of slides to insure a higher degree of interrater reliability.’</td>
<td>Expanded justification below</td>
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<td>25</td>
<td>25</td>
<td>Change from ‘Dermatopathology Panel’ to ‘central dermatopathologist.’</td>
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**Justification:**

Due to complications with the VA contracting process for our three study dermatopathologists, we were unable to use the joint evaluation of all three as our primary diagnosis for CSP562. We ultimately discovered, however, that we could obtain the diagnosis of one of the three, Dr. Robinson-Bostom, for all potential endpoints because of her pre-existing agreements with the VA. We determined that the agreement between her diagnosis and the evaluation of all three for the first 185 biopsies was near perfect agreement, much better than the agreement of the three with the local pathology reading. Hence we seek to substitute Dr. Robinson-Bostom’s diagnosis for the evaluation of the three dermatopathologists originally proposed for the purpose of determining endpoints for CSP562.
4. Original statistical analysis plan V1.0
# Title: Statistical Analysis Plan (SAP)

**MAVERIC Study Specific Documents**

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<tr>
<th>DATE OF ISSUE</th>
<th>DOCUMENT DESCRIPTION</th>
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<tr>
<td>SEPTEMBER 2010</td>
<td>This document describes the statistical analysis plan for the VA KERATINOCYTE CARCINOMA CHEMOPREVENTION randomized clinical trial.</td>
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**AUTHOR:** Robert A. Lew, PhD  
**SUBMITTED BY:** Robert A. Lew, PhD

**DOCUMENT/RECORD HISTORY:**

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<td>09/09/2010</td>
<td>1.0</td>
<td>Initial Version</td>
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**AUTHORIZATION SIGNATURES**

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<tr>
<td>Martin Weinstock MD,</td>
<td>Principal Investigator</td>
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<tr>
<td>Louis Fiore MD, MPH</td>
<td>Study Director</td>
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<tr>
<td>Robert Lew, PhD</td>
<td>Study Biostatistician</td>
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<tr>
<td>Patricia Baldwin MPH</td>
<td>Project Manager</td>
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<tr>
<td>Ryan Ferguson , MPH</td>
<td>Quality Assurance Officer</td>
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</table>
Title: Statistical Analysis Plan (SAP)

1. INTRODUCTION........................................................................................................................................... 3

2. STUDY OBJECTIVES.......................................................................................................................................... 3

3. INVESTIGATIONAL PLAN ............................................................................................................................ 4
   3.1. OVERALL STUDY DESIGN AND PLAN ................................................................................................. 8
   3.2. EFFICACY AND SAFETY VARIABLES ............................................................................................... 9
   3.2.1 Efficacy endpoints.......................................................................................................................... 9
   3.2.2 Safety Variables............................................................................................................................. 12

4. STATISTICAL METHODS ............................................................................................................................ 12
   4.1. STUDY SUBJECTS .................................................................................................................................. 12
   4.1.1 Disposition of Subjects.................................................................................................................. 12
   4.1.2 Analysis Populations...................................................................................................................... 12
   4.2. DEMOGRAPHICS AND BASELINE CHARACTERISTICS ........................................................................ 13
   4.2.1 Demographics................................................................................................................................ 13
   4.2.2 Medical History and Comorbidities ............................................................................................... 13
   4.3. GENERAL CONSIDERATIONS .......................................................................................................... 13
   4.4. EFFICACY EVALUATION ................................................................................................................. 13
   4.4.1 Primary Efficacy Analysis ........................................................................................................... 13
   4.4.2 Secondary Efficacy Analysis ......................................................................................................... 17
   4.4.3 Cost Analysis.................................................................................................................................... Error! Bookmark not defined.
   4.5. SAFETY EVALUATION ....................................................................................................................... 25
   4.5.1 Mortality .......................................................................................................................................... 25
   4.5.2 Adverse Events ............................................................................................................................ 25
   4.6. DETERMINATION OF SAMPLE SIZE .............................................................................................. 26
   4.7. MISSING VALUES ............................................................................................................................ 27
   4.8. MULTIPLEXITY..................................................................................................................................... 27
   4.9. INTERIM ANALYSES ......................................................................................................................... 27
   4.10. DATA MONITORING COMMITTEE ................................................................................................. 28

5. REPORTING OUTPUT ....................................................................................................................................... 28

6. LISTS OF TABLES, FIGURES AND LISTINGS ......................................................................................... 29

7. SUBJECT DISPOSITION SHELLS .............................................................................................................. 31

8. BASELINE CHARACTERISTICS SHELLS ................................................................................................. 35

9. EFFICACY SHELLS ....................................................................................................................................... 40

10. SAFETY SHELLS .......................................................................................................................................... 49
1. **Introduction**

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin, both keratinocyte carcinomas (KCs), account for a half of all cancers in the United States, and over 100,000 cases per year in the VA. Their standard treatment, excision of the lesion, costs the US health care system some $2.5 billion annually and about $100 million annually in the VA. There is no proven means to prevent KCs. An effective prevention strategy would dramatically change the way high risk patients are managed and could substantially reduce the costs of care. We hypothesize that topical 5-fluourouracil (5-FU) chemoprevention will prevent skin cancer and will be cost-saving. To test this we propose a randomized controlled trial of 5-FU compared to a vehicle control to the face and ears. In the study, 1500 veterans at high risk of skin cancer defined as at least 2 KCs in the prior 5 years, at least one of which was on the face or ears, will be randomized to 5-FU or a vehicle control cream, and followed 2 to 4 years. The endpoint will be the incidence of BCCs and SCCs on the face and ears. We will also assess the cost of care, quality of life, and side effects associated with treatment, and the prevalence and number of actinic keratoses, a skin cancer precursor and itself a cause of morbidity and cost. By targeting patients at high risk, the study focuses on high-cost patients for whom this treatment could both improve outcomes (cancers and quality of life) and reduce costs.

2. **Study Objectives**

**Primary Objectives:**

To determine the effect of topical 5-FU treatment (compared to a vehicle control treatment) on reducing surgeries for KC on the face and ears. This is to be determined in high-risk patients in a 4 year trial (2 years recruitment; average follow-up 3 years). Everyone in the trial will receive enhanced patient education and free sunscreen for the duration of the trial.

**Secondary Objectives:**

To evaluate the cost-effectiveness of this intervention, and effect of the 5-FU treatment on the incidence of surgery for BCC, on the incidence of surgery for SCC, on
cryotherapy to the face and ears and prevalence of AKs, on quality of life, and on the frequency and severity of specific side-effects of the treatment.

STUDY OUTCOME MEASURES

A. Primary Outcome:

The primary outcome will be the time to diagnosis of the first KC on the face or ears for which surgery is performed. By requiring surgical treatment, we are focusing on the more consequential lesions associated with morbidity and cost for our primary outcome. It should be noted, however, that we expect approximately 91% of the KCs diagnosed in this study to be treated surgically (based on our VATTC Trial experience), as this is the standard treatment. This outcome uses a time-to-event survival analysis comparing the hazard rates with the two treatments.

B. Secondary Outcomes

Secondary outcomes includes cost-effectiveness, measures of AK’s, quality of life, side effects of treatment, lesion locations, and use of NSAIDS. Also, included are outcomes related to the primary outcome such as,

1. Time to occurrence of first BCC for which surgery is performed, and separately of first SCC for which surgery is performed
2. Number of BCCs, SCCs, and overall KCs requiring surgery per person-year of follow-up
3. Time to occurrence of first KC, BCC, and SCC for which surgery is not performed
4. Surgeries not for KC’s

3. Investigational Plan

1. Both groups:

All participants will receive patient education about skin cancer, including images of typical early skin cancer lesions, and will be counseled on sun protection and the use of sunscreen. Sunscreen will be provided to the participants free of cost for the duration of the trial. All participants will also be given detailed instructions on how to apply the medication, and shown photographs of a patient with a moderate to severe reaction to 5-FU to illustrate a possible reaction to the study medication.
2. **Intervention group:**

The intervention group will have topical 5-FU 5% cream applied twice daily for 4 weeks to the face and ears, to be initiated immediately after randomization. The FDA-approved treatment for AKs is twice daily for 2-4 weeks (28 to 56 total doses), and for superficial BCC is 3-6 weeks twice daily (42 to 84 total doses). These two schedules overlap; for this study the treatment duration will be 4 weeks (56 doses). The 5-FU will only be given once although multiple treatments might potentially be more effective. We expect to be able to detect effectiveness of a single treatment. There are currently no data on which to determine the optimal interval between 5-FU chemopreventive treatments.

We hypothesize that the 5-FU treatment will destroy KC precursors, and because of their slow progression will therefore have a prolonged effect on KC incidence, despite the short course of treatment. The ultimate use of this chemopreventive strategy will undoubtedly involve re-treatment. The data from this study will guide estimation of duration of effect of a single treatment and the appropriate length of a re-treatment interval (see XI.G.1.).

If the participant is unable to tolerate the twice daily 5-FU, they will discontinue the treatment and initiate "cool-down" treatment with triamcinolone 0.1% cream twice daily until the symptoms resolve. In these reactions, symptoms generally resolve within the first 3 days. Asymptomatic erythema typically resolves in about 2 weeks. At 3 weeks after stopping 5-FU, if and only if the participant has not received at least the minimum 2 week (28 dose) course, 5-FU treatment will be resumed on a once-daily basis to complete the 56 dose course. If this is not tolerated, the “cool-down” routine will be followed, but 5-FU will be stopped. It is commonly assumed that the inflammatory response indicates an adequate dose of the topical 5-FU has been received, in which case even those who stop early are likely to benefit from the chemopreventive effect of the experimental cream.

Clinical experience indicates the importance of counseling regarding possible reactions for the successful use of this agent. This counseling will be provided by the on site study nurse, who will talk with all participants at each visit and weekly by phone during the treatment. Study nurses will be trained for counseling prior to use and during use, and for appropriate handling of potential issues that may arise during and after treatment.

B. **Assessment schedule**
Baseline visit:
- Assess inclusion/exclusion criteria (10 mins)
- Review Informed Consent (15 mins)
- Randomization (5 mins)
- Perform complete skin examination (10 mins)
- Baseline Interview to obtain relevant history (30 mins)
- Quality of Life assessment (10 mins)
- Intervention overview (10 mins)

Telephone interview by study nurse (5 min)
- Weekly during intervention phase
- Once every three months during follow up

Brief follow-up visit at 2 and 4 weeks, and every two weeks thereafter if still on treatment
- Brief face/ears only assessment by study nurse (5 mins)
- Study nurse counseling and focused interview (15 mins)
- QOL assessment (10 mins) at 4 weeks

Follow up visits (every 6 months)
- Complete skin examination (10 min)
- Follow up interview (time since last visit) (15 min)
- If a potential skin cancer is to be biopsied, digital photograph to document precise location; if a surgery has been performed on a KC that had not been photographed, the location will be photodocumented
- QOL assessment at 12, 24, and 36 month visit (10 min)

In order to better illustrate the typical assessment schedule for participants in VA CSP 562, the following figures have been included for review.
Figure 1: Typical assessment schedule for a participant in VA CSP 562. Note: Assumes average follow-up time of 3 years as stated in protocol, and no cool down period.
3.1. Overall Study Design and Plan

This trial will be a double-blind, randomized, 4-year, two-arm trial. The trial will test the null hypothesis that the two strategies do not differ with respect to the time-to-event outcome, the first diagnosis leading to surgical treatment of a pathologically confirmed KC lesion.

In terms of the alternative hypothesis we wish to show that:

The 5-FU-based field treatment strategy is effective in the prevention of surgery for a pathologically confirmed KC lesion.
The four-year study can be divided into two periods; namely, a 2-year start-up and enrollment period, a 2-year follow-up period in which patients are only followed. Hence, the length of follow-up time may vary from 2-4 years. Assuming a uniform rate of enrollment the average potential follow-up time will be 3 years.

3.2 Efficacy and Safety Variables

3.21. Efficacy endpoints

PRIMARY HYPOTHESIS

The primary outcome will be the time to diagnosis of the first KC on the face or ears for which surgery is performed. By requiring surgical treatment, we are focusing on the more consequential lesions associated with morbidity and cost for our primary outcome. It should be noted, however, that we expect approximately 91% of the KCs diagnosed in this study to be treated surgically (based on our VATTC Trial experience), as this is the standard treatment. This outcome uses a time-to-event survival analysis comparing the hazard rates with the two treatments.

Since we are evaluating chemoprevention, the primary outcome is surgery for primary lesions, not recurrent lesions. Recurrent lesions are recognized by their occurrence in the scar from prior removal of the cancer. We understand that recurrent lesions occur when malignant cells remain after removal or destruction of a KC, and those cells are frequently deep in the skin and therefore less suitable for treatment with topically applied agents.

This endpoint will be ascertained either at the scheduled follow-up examinations or at examinations requested by the patient. At each study visit, the participant will be questioned about any skin cancers or surgeries. Any potential KCs designated for surgical intervention will be noted for later tracking on Form 10: KC Treatment, and the VA electronic record will be checked to ascertain or confirm the occurrence of the KC and the surgical procedure. For all participants in the trial, all pathology reports of biopsies from the skin of the face or ears will be reviewed at the chairman’s office to determine the diagnosis of all lesions biopsied or otherwise surgically removed, and all of the histopathologic specimens surgically removed lesions will be reviewed by the central dermatopathologists. If a surgically excised lesion has the diagnosis of KC on initial biopsy, subsequent re-excision or Mohs surgery layers slides will not be sent for central review, since the lesion already has a centrally reviewed diagnosis of KC and hence qualifies as an endpoint. Skin cancers diagnosed outside of the VA, and associated surgeries, will be systematically sought in all participants to insure that our outcome measure is complete. For any outside diagnosis or surgery, the medical record will be sought and reviewed. In the VATTC trial, 91% of KCs biopsied had a
subsequent surgical treatment (some variety of excision or electrodessication and curettage), and diagnosis of KCs on the face and ears outside of the VA system represented only 1% of the total number of KCs on the face and ears during that 6-year trial.

We will use actual cancer occurrence for which surgery is performed, as opposed to occurrence of a precursor or intermediate marker, as the primary outcome because of the problems in the in reliability of diagnosis and counting precursor lesions, their variable natural history, which includes a high probability of apparently spontaneous resolution, and a small probability of progression to invasive cancer. The null hypothesis is that the two treatment groups (5-FU intervention and control therapy) do not differ in their time-to-event hazard rates. The alternative hypothesis is that intervention has a lower hazard rate than control therapy with a hazard ratio for control therapy compared to intervention exceeding 1.42.

**NULL HYPOTHESIS**
The null hypothesis is two-sided and thus we would reject the null hypothesis if the hazard ratio exceeded 1.42 or was less than 1/1.42 = 0.7, but only the former event would be deemed a success.

In summary, the design compares two treatments and the study outcome is the first diagnosis leading to surgical treatment of a pathologically confirmed KC lesion.

**SECONDARY OUTCOMES**

1. **Cost-effectiveness of the treatment strategy:** It is common for susceptible individuals to have multiple AKs and KCs. The cumulative resources devoted to their care and specifically the treatment costs are large (see I.B). The cost analysis will therefore look at potential short-term and long-term savings from this strategy in high-risk populations (see VII). KC treatments other than surgery, which are expected to be few, will also be included in this assessment.

2. **Time to occurrence of first BCC for which surgery is performed, and separately of first SCC for which surgery is performed:** The etiologic differences between BCC and SCC indicate that a chemopreventive intervention may have differential effects between the two histopathologic types of KC. As reviewed in Section I, there is substantial evidence that the proposed intervention will be effective for both histologic types. Since there are identifiable populations at greater risk for BCC, and others for SCC, delineating the value for each separately is worthwhile. We will also examine predictors of BCC and SCC occurrence.
3. **Number of BCCs, SCCs, and overall KCs requiring surgery per person-year of follow-up:** Because patients often will have multiple KCs, we will evaluate the number of BCCs, SCCs, and KCs per person-year of follow-up. This may show that the treatment reduces the overall numbers of KC over time.

4. **Time to occurrence of first KC, BCC, and SCC for which surgery is not performed.** This will allow us to determine any effect of the study intervention on a later decision to treat a skin cancer surgically, instead of by an alternative modality. The numbers not treated surgically are expected to be small (about 9% of KCs diagnosed), so only an (unexpected) large effect could be noted in this analysis.

5. **Measures of AKs:** We will also measure AKs because the morbidity and cost associated with these skin lesions is large (see section I). Also, the intervention tested has known efficacy against AKs, so reduced AKs and reduced need for treatment of AKs may be important benefits of the regimen. We will count AKs greater than 5 mm in diameter, a reliable measure. We will also count and measure cryotherapeutic treatments as an outcome; this is the standard treatment for AKs. Cryotherapy treatments will be a component of the cost-effectiveness analysis. Any treatments for AKs other than cryotherapy will also be measured.

6. **Surgeries not for KC:** We will examine whether there is a difference between groups in surgery on the face and ears for lesions other than KC. This will also be a component of the overall cost-effectiveness analysis.

7. **Side-effects of treatment:** Specific indices of chemopreventive treatment side-effects (especially pain, itch, sores/crusts, and erythema) will be ascertained. The measurement will include questions regarding the presence and degree of symptoms such as pain/burning and pruritus of the face and ears as well as erythema.

8. **Quality of life:** Skin cancer can cause substantial anxiety, disfigurement, and other morbidity. For quality of life, we will use the Skindex (a published, validated, widely used quality of life instrument for skin disease). This is a brief questionnaire completed by the participant.

Morbidity from KC may include both morbidity from the cancer and from the treatments. When cancer is diagnosed, treatment of AKs may result in short-term pain and long-term depigmentation that may be disfiguring. Hence the quality of life measure reflects morbidity due to the skin cancers, morbidity due to
AKs, morbidity due to their treatment, and morbidity due to the chemoprevention interventions themselves.

9. **Exploratory analysis of endpoint location:** We will review photographs of endpoint lesions to ascertain any particular sub-areas on the face and ears at which the chemopreventive treatment may have been more or less effective.

10. **Nonsteroidal anti-inflammatory medications (NSAIDs):** We will assess use of NSAIDs (OTC and prescribed) to evaluate their relation to KC risk, since that association has been suggested but is controversial

3.2.2 **Safety Variables**

The safety variables are the serious adverse events; namely death, hospitalization, other SAE's. In addition, safety outcomes include all adverse events related and unrelated to treatment.

4. **Statistical Methods**

4.1 **Study Subjects**

4.1.1 **Disposition of Subjects**

The number of subjects screened, enrolled, and completing the study will be presented overall and by center subdivided by demographic categories (i.e., gender, race, etc.)

Reasons for the early termination of subjects as noted on the CRF will be summarized. Subjects that are lost to follow-up will be summarized as one category.

The following listings will be provided:

- A by-subject listing of completion/termination details
- A by-subject listing of protocol violations and deviations

4.1.2 **Analysis Populations**

All enrolled subjects will be included in the subject listings (by study ID number).
All eligible subjects who gave consent will not be included in the analysis. Only subjects who begin to receive treatment will be included in the safety (safety population) and efficacy (efficacy population) analyses.

4.2 Demographics and Baseline Characteristics

4.2.1 Demographics
Demographic details (e.g., age, sex, ethnicity, race, marital status, and smoking status) will be summarized overall and by center.

4.2.2 Medical History and Comorbidities
The pertinent medical histories (i.e., comorbidities), and history of AKs and skin cancer will be summarized overall and by center. (frequencies and percentages will be given).

4.3 General Considerations
In general the number of observations, mean, median, standard deviation, minimum, and maximum will be calculated for continuous variables. The number of decimals place will be as follows: minimum and maximum to the same number of decimal places as present in the raw data, mean and median to plus one decimal place, standard deviation to plus two decimal places. Frequencies and percentages will be calculated for categorical data.

Baseline is defined as the baseline assessment visit.

Missing endpoint data will not be imputed. Missing covariate data will be imputed in selected circumstances as described below.

All planned analyses for the final clinical study report will be performed using a two-sided nominal significance level of 0.05; however, comparisons less than 0.10 will also be discussed as being marginally significant.

4.4 Efficacy Evaluation

4.4.1 Primary Efficacy Analysis
The study will enroll a total of 1000 patients, 500 of whom will receive the topical 5-FU-based treatment, and 500 of whom will receive the control treatment. We will enroll 500 patients per year for two years to accrue 100 patients per site at 10 VA medical centers.
The outcome measure distinguishes between surgical excisions of a pathologically confirmed KC lesion (either BCC or SCC lesion) and the rare excisions that result in any other diagnosis. Because chemoprevention may have no effect on other lesions, only KC lesions will be counted for the primary outcome.

The primary outcome measure is:

The time after enrollment in the study until the first diagnosis leading to surgical treatment of a pathologically confirmed KC lesion.

In terms of the alternative hypothesis we wish to show that:

The 5-FU-based field treatment strategy is effective in the prevention of surgery for a pathologically confirmed KC lesion.

A. The Primary Outcome:

The null hypothesis is that the two treatment groups (5-FU intervention and control therapy) do not differ in their time-to-event hazard rates. The alternative hypothesis is that intervention has a lower hazard rate than control therapy with a hazard ratio for control therapy compared to intervention exceeding 1.42.

This four-year study will enroll patients for 2 years so that the last patient enrolled will potentially have up to 2 years of follow-up. The first patient enrolled will potentially have up to 4 years of follow-up. On average, patients will potentially have approximately 3 years of follow-up. Thus, the power calculations are based on estimates of a surgically treated diagnosis of KC within 3 years.

Based on the VATTC study we expect the 3-year rate of surgical excision of a pathologically confirmed KC lesion will be 44%. This is a VATTC incidence rate as opposed to a surgery rate, but these will negligibly differ.

We have chosen a 3-year of 42% for the outcome, surgical excision of a pathologically confirmed KC lesion. We make this 2% reduction for several reasons. First, a rare patient who developed both a SCC and a BCC at the same time will only be counted once. Second, in the proposed study, the 3-year incidence rate for KC may be slightly reduced because of differences between the old VATTC protocol and the proposed protocol. In the proposed trial physicians will adhere to their internal policies and tend to systematically remove many of AK’s with cryotherapy and thereby may lower the 3-year KC rates. In the VATTC trial, centers were asked to take a watchful waiting policy on most AK’s, but tended to follow their own internal policies on this matter. Third, for the proposed trial we will
exclude patients who had 5-FU treatment during the 3 years prior to enrollment, and we speculate that these patients may be at higher risk for KC’s than the eligible patients. To account for these three factors we assume that the KC rate for the proposed trial will be 95% of the VATCC rates.

Under the null hypothesis:

The three-year KC surgery rate will be 42%

Under the alternative hypothesis for patients treated with 5-FU:

The three-year KC surgery rate will be 32%

The reductions attributed to treatment may be viewed in several ways. The absolute reduction from 42% to 32% is 10%, the relative reduction is \((42 - 32)/42 = 24\%\), and the hazard ratio (control hazard rate/treatment hazard rate) of 1.42 midway between the simple odds ratio, \(42(100 - 32)/(32(100 - 42)) = 1.54\) and the risk ratio \(42/32 = 1.31\).

Sample Size and Statistical Power Considerations

The results for the KC primary outcome measure, time until first SCC diagnosis, will be analyzed by means of the two-sided log-rank test to detect either a hazards ratio that exceeds 1.42 or is less than \(1/1.42 = 0.74\). The test will have a two-sided 4.8% type I error. (When added to the interim analysis that has a 0.2% Type I error, the overall type I error is 5%). The test has 90% power to detect a ratio of hazards of 1.36 or larger or 0.70 or less with a total of 1000 patients, 500 per study arm. This assumes that 8% of the patients either die or are lost to follow-up while on-study before a SCC diagnosis can be observed. The power for the log-rank test was computed using Schoenfeld’s formula (see equation 18.10 in Buyse, Staquet and Sylvester, 1984).

Interim Analysis

We will perform one interim analyses when the first 500 patients (250 in each study arm) enrolled have completed two years of follow-up. Assuming a uniform rate of enrollment over time this interim analysis should take place at the end of year 3. With an 8% loss-to-follow-up rate each study arm will have 210 evaluable patients.

The one interim analysis carried out when the 500\(^{th}\) patient completes two years of follow-up has a small effect on overall type I error. The interim analysis has a Type I
error of 0.2%. The interim analysis is two-sided, but the interim null hypothesis will only be rejected if the hazard ratio exceeds 2.39. If the hazard ratio is less than $1/2.39 = 0.42$ then trial will be stopped for futility.

After 3 years the first patient entered will potentially have 3 years of follow-up and the last patient entered will potentially have 1 year of follow-up. Thus, the average potential follow-up will be two years. If we expect a 44% KC rate at three years then under the exponential model we would expect a 32% KC rate at two years.

Under the interim analysis null hypothesis:

The two-year KC rate will be 32%

Under the interim alternative hypothesis for patients treated with 5-FU:

The three-year KC rate will be 16%

The reductions attributed to treatment may be viewed in several ways. The absolute reduction from 32% to 16% is 16%, the relative reduction is $(32 – 16)/32 = 50\%$, and the hazard ratio (control hazard rate/treatment hazard rate) is 2.39.

We considered earlier times for interim analyses, but rejected this idea because sample sizes on the order of 150 per study arm only have modest power to detect very large effects.

For both the interim analysis and the primary analysis we considered the possibility that the effect of 5-FU merely delays the clinical emergence of a KC by a short period, such as 6 months. Then a wide gap between control and treatment arms, due to lower incidence in the treatment arm, might rapidly narrow with more follow-up. Indeed, this possibility led us to propose to monitor VA electronic records and passively follow patients after the four-year study ends to detect such narrowing. Finally, compared to other types of cancer KC’s are seldom fatal, so that the evaluation of costs to the VA and patient morbidity assume greater importance. We expect that to gather the data for these evaluations would prolong the trial past the early stopping date.

Data Analysis Plan

The primary outcome hypothesis will be tested using a two-sided log-rank test to compare the hazard rate for one treatment group to that for another treatment group. A significant difference showing that the intervention strategy compared to the control decreases the hazard of surgery for pathologically confirmed KC will be regarded a
positive result, whereas a result that shows intervention does not significantly differ from or, in fact, significantly increases the hazard rate will be regarded as a negative result. We will report the hazard rates, their ratio and the 95% confidence interval about the ratio. This will be followed by further refined analyses, using multiple linear Cox proportional hazards regression modeling, to take account of the effects of baseline covariates on the primary outcome measure. Covariates will include demographic and clinical factors (age, sex, smoking status, education, number of AK's, history of BCC, of SCC, or both).

The regression modeling we shall employ will include a model with treatment by covariate terms to explore the possibilities of treatment by covariate effects (that is, exploration of potential subgroup effects). We will test the proportional hazards assumption by including a time-treatment interaction term in the model. We will use graphic methods to study goodness-of-fit as described in section VII.3.1 of the text 'Statistical Models based on Counting Processes (Anderson K, Borgan O, Gill RD, and Keiding N, Springer-Verlag New York 1991).

Extended Follow-Up

The four-year study can be divided into two periods; namely, a 2-year start-up and enrollment period, a 2-year follow-up period in which patients are only followed. Hence, the length of follow-up time may vary from 2-4 years. Assuming a uniform rate of enrollment the average potential follow-up time will be 3 years.

The power calculations account for both the varying amount of follow-up time and for the censoring of outcomes. Varying follow-up time and the length of the recruitment period have negligible effects on power. We have assumed an 8% rate of lost-to-follow-up combining the on-study death rate with the study lost-to-follow-up rate. Hence, the statistical power calculation is based on the 920 evaluable patients among the total of 1000 enrolled.

When the study ends after 4 years we will continue for one year to follow patients who have not had a new KC surgery by tracking the medical procedures they have as reported in the VA Austin database. We will look for an excess of KC surgical events in the 5-FU treatment arm indicative of events delayed by treatment as opposed to prevented by treatment.

4.4.2 Secondary Efficacy Analysis
Secondary analyses are of several types; analyses directly related to the primary hypothesis of BCC and SCC surgical endpoints, quality of life as measured by the Skindex instrument, multiplicity of AK’s, and cost analyses. Cost analyses are described in section VII.

Time to surgery for a new BCC and for a new SCC:

In analyses directly related to the primary hypothesis, we will disaggregate KC into its components BCC and SCC. Then we will compare the treatments with respect to each of the two separate outcomes of the time to a diagnosis leading to surgery for a new SCC and time to a diagnosis leading to surgery for a new BCC using the analogous time-to-response analysis delineated for the primary analysis. For this secondary outcome each of the two parallel null hypotheses is that the two treatment groups (intervention and control therapy) do not differ in their time-to-event hazard rates. As in the primary analysis, we will begin with the two-sided log-rank test for each of the two outcome measures, time until the first BCC diagnosis leading to surgical treatment of a pathologically confirmed SCC lesion and time until the first BCC diagnosis leading to surgical treatment of a pathologically confirmed BCC lesion.

We will carry out two additional time-to-event analyses of the aggregated KC outcome. We will apply the log-rank test to the data obtained from the extended follow-up beyond 4 years as in the primary analysis. This analysis will be done on both the final data set when the trial ends and on the extended follow-up data set. For each of these analyses we will report the hazard rates, their ratio and the 95% confidence interval about the ratio. This will be followed by further refined analyses, using multiple linear Cox proportional hazards regression modeling, to take account of the effects of baseline covariates on the primary outcome measure. Covariates will include demographic and clinical factors (age, sex, smoking status, education, number of AK’s, and history of BCC, of SCC, or both. The regression modeling we shall employ will include a model with treatment by covariate terms to explore the possibilities of treatment by covariate effects (that is, exploration of potential subgroup effects).

These secondary analyses are exploratory in nature and thus we have not assigned it a level of power. Extensive exploratory analyses will address the issue of the optimal time interval between applications of 5-FU therapy. Assuming that one 5-FU treatment reduces the hazard of surgical outcomes, we will separately study the disease endpoints of BCC, SCC, and KC to determine the shape of the hazard rate over time for the 5-FU treated and control patients. The objective will be to estimate the hazard rate for a new BCC, SCC, or KC in the treated and untreated groups. We will use an extension of the proportional hazards model, specifically with a Weibull frailty model that provides an explicit model for the hazard rate. In particular, we will test whether the hazard rate for patients treated with 5-FU remains flat or rises over time. This would
address the question of whether 5-FU treatment delays the incidence of new KC’s.
Relative to the hazard rate among controls and to a flat hazard rate, the pattern of a rising hazard rate over time would indicate that 5-FU delayed KC incidence. If 5-FU is effective then the pattern of a flat hazard rate over time would indicate destruction of a proportion of KC’s but not delay.

Quality of Life:
We will compare the treatments with respect to the change in the Skindex score after one year and after two years. The change after one year is the difference between the one-year score and the baseline score. The change after two years is the difference between the two-year score and the baseline score. Regarding these changes as continuous outcomes, we will use Student’s t-test to compare the treatments. Controlling for the covariates listed above we will carry out a linear regression analysis with treatment as the major factor. Confirmatory analysis will be done using combining the one-year, two-year, and three-year change scores into a repeated measures regression analysis. This analysis will treat the factor subject as a random effect and explore the possibility of different sizes of effect within each follow-up year.

Burden of Actinic Keratoses:
We will evaluate the effect of study treatment on the burden of actinic keratoses on the face and ears, as assessed by counts of large lesions, >= 5 mm in diameter. For the analyses of counts and for the number of spot treatments we will fix the follow period at two years and carry out a simple Poisson regression comparing the treatments and a more complex Poisson regression comparing the treatments and controlling for covariates. For the analyses of estimates of skin area affected (a continuous outcome) we will fix the follow period at two years and carry out a Student’s t-test comparing the treatments and a more complex linear regression comparing the treatments and controlling for covariates. To confirm this analysis we will collapse the Poisson counts into ordinal categories; none, 1-3, 4-10, 10 or more. We will rerun the analysis using polychotomous logistic regression. For each of the proposed analyses viewing baseline and each follow-up year as repeated measures we will also analyze the data with subject as a random effect using the SAS procedure NLMIXED.

4.4.3 Cost analyses
Cost-effectiveness of the treatment strategy: It is common for susceptible individuals to have multiple AKs and KCs. The cumulative resources devoted to their care and specifically the treatment costs are large. The cost analysis will therefore look at potential short-term and long-term savings from this strategy in high-risk
populations (see VII). KC treatments other than surgery, which are expected to be few, will also be included in this assessment.

Design Considerations for the Economic Analysis:

There are two components of the proposed economic analysis. First, we will conduct a cost-effectiveness analysis from both a VA and a societal perspective. Second, we will conduct a business impact, or cash-flow analysis from a VA perspective. The purpose of this second analysis will be to provide VA managers with the information that they need to accurately determine the financial impacts of adopting the study protocol as standard therapy. Both of these analyses are conditional on the main outcome of the study being an effective intervention. If the intervention doesn’t work, the economic analyses are moot, as the intervention will not be clinically adopted.

Skin cancer is a condition for which the treatment can be clearly separated from the treatment of other conditions. Thus, this study will not consider other health care costs; we will assume that the randomization equalizes these across the two study arms. The one exception to this is if a skin cancer metastasizes to another site. The costs and utilization associated with the treatment of metastatic cancers will be considered, conditional on site investigator verification that the metastatic cancer is related to BCC or SCC.

Preliminary calculations based on the effect sizes that the study is powered on project a cost savings associated with the intervention. Further, these cost savings will persist for a wide range of assumptions about the costs of therapy and the effectiveness of the intervention. Thus, there will only be conditional collection of health utilities information. If the initial analysis at the end of the trial show that we need to value the relevant health state utilities, we will submit a supplemental proposal to CSSMRB for the collection of health utilities. Study information from the skin cancer-specific quality of life measures collected during the study, will be used to determine the health states that need to be valued. Community ratings will be obtained for these health states. Since study subjects are not required for this method of utility assignment, the collection of the utility data can be deferred without jeopardy to the proposed analysis.

Sources of Cost and Utilization Data

VA costs will be captured from the VA Decision Support System (DSS) National Data Extracts (NDEs). DSS is a comprehensive, activity-based hospital accounting system that VA uses to track its costs. Summary extracts are made from this system that tract inpatient, outpatient, and pharmacy costs. These data are extracted and converted to
SAS datasets at the VA Austin Automation Center (ACC) on an annual basis. They are usually available in February of each year.

Encounter data with ICD-9-CM codes for all encounters, and CPT codes for outpatient encounters are also available from the National Patient Data Base SE file at the ACC. These data will allow centralized tracking of all VA patient care encounters.

At many VA facilities at least some of the skin cancer-related care (especially Mohs surgery) is provided as contract care. To ensure complete data for this care, each site will be asked to identify the types of care that they routinely provide under contract or fee-basis care. Study forms will be used to capture the CPT codes for all fee-basis and contract care. While there are centralized databases of fee basis care, these data have never been carefully assessed for completeness. Further, starting in FY 2007, all fee-basis and contract care is supposed to be captured by DSS. Once the FY 2007 DSS extracts are available in early 2008, HERC will compare the data reported on the study forms with the fee-basis and contract care reported in DSS. If the DSS is found to accurately capture these data, use of the study forms for contract and fee-basis care will be discontinued.

Non-VA Health Care

Prior experience from CSP #402 found that 99% of the KC-related care was VA provided. Thus, while patients will be asked to self-report their use of related care obtained from a non-VA provider, the impact of errors of patient self-reporting will be minor. At enrollment, patients will be asked to bring copies of the billing statements for any non-VA skin cancer-related care to each subsequent follow-up visit. At each follow-up visit, the site coordinator will ask the patient if any non-VA skin cancer-related care was received since the last visit. If the patient does not provide copies of the billing statements, the site coordinator will use a study form to determine what non-VA care was provided. Fortunately, there are only a few types of patient care encounters that are relevant care. Thus, the study form will list each of the types of service. VA averages for these types of encounters will be used to assign costs to these encounter types. Patients will also be asked for the date of service. These self-reported uses of non-VA care will be cross-checked with the VA databases, especially the fee-basis files, to prevent double counting.

Patients will also be asked at enrollment if they are currently enrolled in Medicare (median age for CSP #402 was 71). If they are not currently enrolled in Medicare, they will be asked if they expect to enroll in Medicare during the study period. The consent form will include permission to access Medicare records. A finder file of all study patients will be submitted to VIREC, which is the VA repository of the Medicare data for users of VA care. These Medicare data will be used as a further check for study
relevant non-VA health care utilization. Given the lag in the linking of the Medicare data to VA users, the Medicare data may not be available for the last year of the study at the time of analysis. But, the Medicare data will provide data for earlier years of follow-up and allow the assessment of the completeness of the patient self-report of use of non-VA care.

**Assumptions for Preliminary Cost Analysis:**

The VA cost of 5-FU was obtained from the April 2007 list of current VA drug prices maintained by the VA Pharmacy Benefits Management (PBM) group. It was assumed that two 40g tubes of 5-FU would be sufficient for each course of chemo-preventive therapy. The April 2007 cost of a 40g tube of 5-FU was $80.42, yielding a per treatment cost of $160.84. The CPT codes were identified for Mohs facial surgery, and the 2005 VA frequency of use of these codes identify their relative use in VA. Using 2006 Medicare RVUs, conversion factors, and APC facility payment rates, we calculated an average cost of $830. This cost decreases to $715 if the surgery is done in conjunction with one of the more expensive types of reconstructive surgeries due to the facility payment methodologies for ambulatory surgery.

To estimate the VA costs for reconstructive procedures, we examine the “repair” codes recorded in VA encounters where Mohs surgery was performed. We used the weighted average of these payments, with adjustments for the Medicare facility payment methodology to obtain a weighted average VA cost for Mohs surgery and reconstruction of $1573.

Based on the information from CSP 402 and a search of centralized VA data, we know that the patients who will be enrolled in this trial have a high incidence of AK, which will almost always be treated with cryosurgery. Again, we used the actual VA use of CPT codes to calculate a weighted average cost for a cryosurgery of $138.

While it is possible that the intervention will reduce other VA costs of care, no other potential savings were included for this preliminary analysis. We acknowledge that there will probably be some added costs of the intervention for following up with patients by telephone during the intervention period. These will be captured during the actual analysis, with care to make sure that they exclude the additional visits/contacts that were part of the research project, not actual patient care. The cost of the initial visit at which the 5-FU is dispensed will not be included as this would be done at a regularly scheduled annual encounter for these high-risk patients.

From the power calculation of this trial, we are conservatively projecting an absolute reduction of 11% in the number of KC that will require surgical treatment. For the base analysis, we also assumed that on average, 0.75 cryotherapy treatments per patient
would be averted. This is a fairly conservative assumption, given that 5-FU is known to be an effective therapy for AK and the study patients average more than 1 AK per year, with an average follow-up of 3 years. These assumptions result in a net savings of $116.

We also tested the sensitivity of these assumptions. If no reductions in AK therapy are assumed, the net savings, due solely to the reduction in Mohs surgery is $13. With the 0.75 cryotherapy treatments averted per patient for the treatment of AK, there are net savings as long as the reduction in the need for surgical treatment for facial KC is greater than 3.6%. Net savings also remain with 0.5 cryosurgeries averted per patient as long as the reduction in surgical treatment for facial KC is at least 5.8%.

The cost-effectiveness analysis will be an intent-to-treat analysis, using an incremental cost-effectiveness ratio, and a societal perspective. All costs and benefits will be discounted at a 3% rate. We will monitor the development of the emerging concept of presenting the results in terms of a net health benefit, and will consider this method as an alternative for presenting the results. Essentially, we are acknowledging that this new method could change the consensus on how to report cost-effectiveness studies, and that we will be sensitive to this possibility.

Because this is a VA trial, the cost-effectiveness analysis will be repeated from a VA perspective. This will be done by revising the final analysis to only include the costs directly incurred by VA. This will have no affect on the QALY expressed benefit to the study subjects.

Given the strong prior that the study results will show the intervention to be effective and have a net cost savings (i.e. strong dominance), the utility/QALY assessment will be conditional. The changes in net health utilities associated with the different therapies in this study are likely to be relatively small. Standard indirect utility instruments such as the HUI and the EQ-5D are unlikely to be sensitive enough to detect these changes. The study will regularly collect data using disease-specific quality of life instruments. These instruments will provide sufficient information to allow the characterization of the health states that are most relevant to the study. If the initial analysis at study close-out shows that the net costs of the intervention may be positive, then supplemental funding will be requested to allow the outcomes from the disease-specific quality of life instruments to be mapped to utilities. These utilities will be assigned using a community sample of healthy adults. The study economist has prior experience with this method; he worked with colleagues at Stanford University to obtain community-rated utilities for the Activities of Daily Living scores that were used to measure patient functioning for Geriatric Evaluation and Management patients in CSP #006. Application of this method will allow utilities to be assigned to the disease-specific quality of life measures that will be recorded for study subjects at regular intervals. The advantage of this approach is
that it avoids the significant expense of assigning utilities to health states unless it is necessary for the completion of the analysis.

We also acknowledge the possibility that the interventions have differential effects on patient quality of life that could be the opposite of our expectations. The intervention will treat all patients to prevent the occurrence of KC in some patients (the intervention will also prevent the occurrence of AK in a larger fraction of patients). Thus, all of the intervention patients will experience some disutility associated with the treatment, while only a subset will receive the utility benefits of averted KC or AK. While the hypothesis is that the intervention arm will result in net higher disease-specific quality of life ratings, we will examine the results to confirm this. If the results of the disease-specific quality of life ratings don’t clearly show a net benefit to the intervention arm, this would also trigger the collection of utilities data from a community sample.

**Cash-Flow Analysis:**

The VA is operated on a fixed global budget. VA managers must make decisions on where and how to allocate fixed resources. While traditional clinical trials results can make a compelling case about the effectiveness of an intervention, they don’t provide all of the information that managers need to implement the adoption of new technologies or treatments. Even if this study has the expected outcome of a net savings attributable to the intervention, this alone will not provide sufficient information for VA managers. This is because the study intervention requires an up front investment in chemo-preventive therapy. The up front costs will not be fully recouped in the first year. To allow VA managers to adequately plan for the adoption of chemo-preventive 5-FU therapy, we also plan to use the study data to calculate the expected cash flow affects of implementing the study intervention. We will use the actual utilization of care for patients in the control arm of the study to project when the averted treatments would have occurred, in terms of months since initiation of 5-FU treatment. These will be summarized on a quarterly basis, and compared with the cost of 5-FU therapy.

HERC has planned to include this type of cash-flow analysis in other CSP trials that are already in progress. The intent is to work with various VA leadership organizations to help disseminate this information. If this trials shows the intervention is effective, we will build on these previous management dissemination efforts. The purpose of this type of analysis is to make the results as useful as possible for VA managers. Feedback from this type of effort for other CSP trials will be incorporated into the exact dissemination plan.
4.5 Safety Evaluation

All safety summaries will be based on the Safety Population described in Section 4.1.2 “Analysis Populations.”

4.5.1 Mortality

The frequency and proportion of all deaths will be presented overall and by center.

A by-subject listing will be provided.

4.5.2 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 9.0) coding dictionary.

All AE summaries will be based upon the number of subjects reporting AEs and not the number of events reported. Adverse events (AEs) will be tabulated (i.e., those events that were not present at the baseline evaluation or worsened in severity following the start of treatment). Any AEs starting after study completion or withdrawal will not be tabulated.

If the AE start date is not a complete date, the following rules will be applied to determine whether the AE will be tabulated or not.

If the start date is completely missing:
- The AE will be tabulated unless the AE stop date is less than the baseline date.

If the day part of the AE start date is missing, use the following algorithm:
- If the month and year of the start date are later than or equal to the month and year of the surgery, then the AE will be tabulated. If the month and year of the stop date are earlier than the month and year of the surgery, then the event will be assumed to not be tabulated.

If the day and month of the start date are missing, use the following algorithm:
- If the year of the start date is later than or equal to year of the surgery, then the AE will be tabulated. If the year of the stop date is earlier than the year of the surgery, then the event will not be tabulated.
The number and percentage of subjects with AEs through the end of the study (analysis period) will be summarized by system organ class and preferred term overall.

Summaries of AEs by intensity and relation to study device will be presented by system organ class and preferred term overall. For each subject and each AE, the worst intensity/relation recorded will be attributed and used in the intensity/relation summaries. If intensity/relation is missing, the intensity/relation will be queried by data management.

The number and percentage of subjects with serious adverse events (SAE) through the end of the study (or analysis period) will be summarized by system organ class and preferred term overall.

A by-subject listing of all AEs will be provided.

A by-subject listing of all serious AEs will be provided.

4.6 Determination of Sample Size for the Primary Hypothesis

The results for the KC primary outcome measure, time until first SCC diagnosis, will be analyzed by means of the two-sided log-rank test to detect either a hazards ratio that exceeds 1.42 or is less than 1/1.42 = 0.74. The test will have a two-sided 4.8% type I error. (When added to the interim analysis that has a 0.2% Type I error, the overall type I error is 5%). The test has 90% power to detect a ratio of hazards of 1.36 or larger or 0.70 or less with a total of 1000 patients, 500 per study arm. This assumes that 8% of the patients either die or are lost to follow-up while on-study before a SCC diagnosis can be observed. The power for the log-rank test was computed using Schoenfeld’s formula (see equation 18.10 in Buyse, Staquet and Sylvester, 1984).
4.7 Missing Values Primary Analysis

Dropouts will be included in the primary analysis assuming random censoring but sensitivity analyses will address their potential that non-random censoring patterns biased the results. Imputation of final outcomes requires questionable assumptions about treatment effects. We will consider a range of such assumptions in the confirmatory analyses. The confirmatory secondary analysis including the dropout data censored at the appropriate study visit will also be done to assess potential bias associated with the complete case analysis.

A covariate adjusted primary analysis will be done in order to either confirm or not confirm the primary analysis that has no covariates. In either case, the confirmatory analysis will indicate the degree of bias in the complete case analysis.

Practical measures will be taken to minimize missing values and losses to follow-up. One prominent conjecture about patients who drop out is that they tend to have poor outcomes. This clearly would violate the assumption of missing-at-random.

Multiplicity

There will be no corrections done for multiple comparisons in this descriptive study.

4.8 Interim Analyses

We will perform one interim analyses when the first 500 patients (250 in each study arm) enrolled have completed two years of follow-up. Assuming a uniform rate of enrollment over time this interim analysis should take place at the end of year 3. With an 8% loss-to-follow-up rate each study arm will have 210 evaluable patients.

The one interim analysis carried out when the 500th patient completes two years of follow-up has a small effect on overall type I error. The interim analysis has a Type I error of 0.2%. The interim analysis is two-sided, but the interim null hypothesis will only be rejected if the hazard ratio exceeds 2.39. If the hazard ratio is less than 1/2.39 = 0.42 then trial will be stopped for futility.

After 3 years the first patient entered will potentially have 3 years of follow-up and the last patient entered will potentially have 1 year of follow. Thus, the average potential follow-up will be two years. If we expect a 44% KC rate at three years then under the exponential model we would expect a 32% KC rate at two years.

Under the interim analysis null hypothesis:

The two-year KC rate will be 32%

Under the interim alternative hypothesis for patients treated with 5-FU:
The three-year KC rate will be 16%

The reductions attributed to treatment may be viewed in several ways. The absolute reduction from 32% to 16% is 16%, the relative reduction is \((32 - 16)/32 = 50\%)\), and the hazard ratio (control hazard rate/treatment hazard rate) is 2.39.

We considered earlier times for interim analyses, but rejected this idea because sample sizes on the order of 150 per study arm only have modest power to detect very large effects.

For both the interim analysis and the primary analysis we considered the possibility that the effect of 5-FU merely delays the clinical emergence of a KC by a short period, such as 6 months. Then a wide gap between control and treatment arms, due to lower incidence in the treatment arm, might rapidly narrow with more follow-up. Indeed, this possibility led us to propose to monitor VA electronic records and passively follow patients after the four-year study ends to detect such narrowing. Finally, compared to other types of cancer KC’s are seldom fatal, so that the evaluation of costs to the VA and patient morbidity assume greater importance. We expect that to gather the data for these evaluations would prolong the trial past the early stopping date.

4.9 Data Monitoring Committee

Data and study progress will be monitored by the study executive committee and by the study steering committee. The Data Monitoring Committee will review the study progress and safety on at least an annual basis with additional meetings and communications as needed..

5.0 Reporting Output

All outputs will be produced using SAS Version 9.1 or a later version (if available at MAVERIC). The REPORT procedure will be used to produce all tables and listings whenever possible. The GPLOT and/or GCHART procedure will be used to produce all figures whenever possible. All statistical appendices (supportive SAS output) will be output directly from the appropriate SAS procedure.

All tables, listings, and statistical appendices will be produced to landscape orientation and will be incorporated into a Word 2003 document (margins: top 1.5”, left, right and bottom 1”) using Courier New 9pt font.
Tables, listings, and figures will be arranged in the order that they appear in the textual sections of this analysis plan, i.e., disposition first, followed by baseline summaries, efficacy summaries, and safety summaries.

All recorded data will be listed following the order and structure of the CRF. In addition, selected derived data used in the analyses will be listed. The listings will include all enrolled subjects (with data relevant to the particular listing) and will be ordered by center, subject, and visit.

6.0 Lists of Tables, Figures and Listings

Subject Disposition
Table XX. Summary of Disposition (Enrolled Subjects)
Listing XX. Completion and Termination (Enrolled Subjects)
Listing XX. Protocol Violations (Enrolled Subjects)
Listing XX. Other Deviations Failures (Enrolled Subjects)

Baseline Characteristics
Table XX. Summary of Demographics (Enrolled Subjects)
Table XX. Summary of Comorbid Conditions and Relevant Medical History (Enrolled Subjects)
Table XX. Summary of Baseline Characteristics - Endpoints (Enrolled Subjects)
Listing XX. Demographics (Enrolled Subjects)
Listing XX. Comorbid Conditions and Relevant Medical History (Enrolled Subjects)
Listing XX. Baseline Characteristics - Endpoints (Enrolled Subjects)

Efficacy
Primary Efficacy Endpoints:
Table XX. Summary of Primary Endpoints (Enrolled Subjects); Overall
Table XX. Summary of Primary Endpoints (Enrolled Subjects); by Center
Listing XX. Primary Efficacy Endpoints (Enrolled Subjects)

Secondary Efficacy Endpoints:
Table XX. Summary of Secondary Endpoints - HRQOL (Enrolled Subjects); Overall
Table XX. Summary of Primary Endpoints - PE (Enrolled Subjects); Overall
Listing XX. Secondary Efficacy Endpoints (Enrolled Subjects)

Tertiary Efficacy Endpoints:
Table XX. Summary of Tertiary Endpoints (Enrolled Subjects); Overall
Table XX. Summary of Medication Use (Enrolled Subjects); Overall
Title: Statistical Analysis Plan (SAP)

Safety
Table XX. Summary Table of AE’s (Enrolled Subjects); Overall
Table XX. Summary Table of SAE’s (Enrolled Subjects); Overall
Listing XX. Listing of all AE’s (Enrolled Subjects); Overall
Listing XX. Listing of all SAE’s (Enrolled Subjects); Overall
7.0 **Subject Disposition Shells**
### Table XX
Shell Table for Subject Disposition (Overall and by Center)

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<td>xx</td>
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<tr>
<td>xx (xx.x%)</td>
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<td>(xx.x%)</td>
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<td>(xx.x%)</td>
<td>(xx.x%)</td>
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<tr>
<td>Early Termination</td>
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<td>xx (xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
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<tr>
<td>Loss-to-follow-up</td>
<td>xx</td>
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<td>xx</td>
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<td>xx (xx.x%)</td>
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<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
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<tr>
<td>Investigator Removal</td>
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<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
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<tr>
<td>Death</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
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<td>xx</td>
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<tr>
<td>xx (xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
</tr>
<tr>
<td>Other</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td>xx (xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
<td>(xx.x%)</td>
</tr>
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</table>

Listing XX
Shell Listing for Completion and Termination of Enrolled Subjects

<table>
<thead>
<tr>
<th>Subject ID Number</th>
<th>Age</th>
<th>Sex</th>
<th>Complete Study?</th>
<th>Date of Completion</th>
<th>Date of ET</th>
<th>Reason for ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>xxx001</td>
<td>xx</td>
<td>m/f</td>
<td>y/n</td>
<td>MMDDYYYY</td>
<td>MMDDYYYY</td>
<td>xxxxx</td>
</tr>
<tr>
<td>xxx002</td>
<td>xx</td>
<td>m/f</td>
<td>y/n</td>
<td>MMDDYYYY</td>
<td>MMDDYYYY</td>
<td>xxxxx</td>
</tr>
<tr>
<td>xxx003</td>
<td>xx</td>
<td>m/f</td>
<td>y/n</td>
<td>MMDDYYYY</td>
<td>MMDDYYYY</td>
<td>xxxxx</td>
</tr>
<tr>
<td>xxx004</td>
<td>xx</td>
<td>m/f</td>
<td>y/n</td>
<td>MMDDYYYY</td>
<td>MMDDYYYY</td>
<td>xxxxx</td>
</tr>
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</table>

Listing XX
Shell Listing for Protocol Violations (Enrolled Subjects)

<table>
<thead>
<tr>
<th>Subject ID Number</th>
<th>Age</th>
<th>Sex</th>
<th>Date of Protocol Violation</th>
<th>Reason for PV</th>
<th>Kept in Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>xxx001</td>
<td>xx</td>
<td>m/f</td>
<td>MMDDYYYY</td>
<td>xxxxxxxx</td>
<td>y/n</td>
</tr>
<tr>
<td>xxx002</td>
<td>xx</td>
<td>m/f</td>
<td>MMDDYYYY</td>
<td>xxxxxxxx</td>
<td>y/n</td>
</tr>
<tr>
<td>xxx003</td>
<td>xx</td>
<td>m/f</td>
<td>MMDDYYYY</td>
<td>xxxxxxxx</td>
<td>y/n</td>
</tr>
</tbody>
</table>
Shell Listing for Device Failures (Enrolled Subjects)

<table>
<thead>
<tr>
<th>Subject ID Number</th>
<th>Age</th>
<th>Sex</th>
<th>Date of Device Failure</th>
<th>Device Failure Description</th>
<th>Failure Type</th>
<th>Did Failure cause an AE?</th>
<th>Kept in Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>xxx001</td>
<td>xx</td>
<td>m/f</td>
<td>MMDDYYYY</td>
<td>xxxxxxx</td>
<td>y/n</td>
<td>y/n</td>
<td></td>
</tr>
<tr>
<td>xxx002</td>
<td>xx</td>
<td>m/f</td>
<td>MMDDYYYY</td>
<td>xxxxxxx</td>
<td>y/n</td>
<td>y/n</td>
<td></td>
</tr>
<tr>
<td>xxx003</td>
<td>xx</td>
<td>m/f</td>
<td>MMDDYYYY</td>
<td>xxxxxxx</td>
<td>y/n</td>
<td>y/n</td>
<td></td>
</tr>
</tbody>
</table>
8.0 Baseline Characteristics Shells
### Table XX

**Shell Table for Baseline Demographics (Enrolled Subjects)**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total (n=XX)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td>Mean / SD</td>
<td>xx.x / xx.x</td>
<td>xx.x / xx.x</td>
<td>xx.x / xx.x</td>
<td>xx.x / xx.x</td>
<td>xx.x / xx.x</td>
<td>xx.x / xx.x</td>
<td>xx.x / xx.x</td>
</tr>
<tr>
<td>Median</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>Range</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
<td>xx.x</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Female</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Race</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Asian</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Native Hawaiian or Pacific</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
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<tr>
<td>Islander</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Other</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
</tr>
<tr>
<td>Martial Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
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<tr>
<td>Single</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
<td>xx (xx.x%)</td>
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</table>
Title: Statistical Analysis Plan (SAP)

Separated

Divorced

Widowed

Table XX
Shell Table for Baseline Characteristics (Enrolled Subjects)

<table>
<thead>
<tr>
<th>Total (n=XX)</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Site</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>E</td>
</tr>
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Family Members with Obesity

Comorbid Conditions

Hypertension

Coronary Artery Disease

Heart Failure

Diabetes

Gall Stones or Colecystectomy

Asthma

Liver disease

Hepatitis B

Hepatitis C

NASH
# Listing XX

## Shell Listing for Baseline Demographics (enrolled subjects)

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Age</th>
<th>Sex</th>
<th>Ethnicity</th>
<th>Race</th>
<th>Marital status</th>
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<tbody>
<tr>
<td>xxx001</td>
<td>xx</td>
<td>m/f</td>
<td>xxxxxxx</td>
<td>xxxxx</td>
<td>xxxxxxxxxx</td>
</tr>
<tr>
<td>xxx002</td>
<td>xx</td>
<td>m/f</td>
<td>xxxxxxx</td>
<td>xxxxx</td>
<td>xxxxxxxxxx</td>
</tr>
<tr>
<td>xxx003</td>
<td>xx</td>
<td>m/f</td>
<td>xxxxxxx</td>
<td>xxxxx</td>
<td>xxxxxxxxxx</td>
</tr>
</tbody>
</table>
### Listing XX

**Shell Listing for Baseline Characteristics (enrolled subjects)**

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Family Member</th>
<th>Obese</th>
<th>HTN</th>
<th>CAD</th>
<th>HF</th>
<th>Other</th>
<th>Other(specify)</th>
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<tbody>
<tr>
<td>xxx001</td>
<td></td>
<td>y/n</td>
<td>y/n</td>
<td>y/n</td>
<td>y/n</td>
<td></td>
<td>y/n</td>
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<tr>
<td>xxx002</td>
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<td>y/n</td>
<td>y/n</td>
<td>y/n</td>
<td>y/n</td>
<td></td>
<td>y/n</td>
</tr>
<tr>
<td>xxx003</td>
<td></td>
<td>y/n</td>
<td>y/n</td>
<td>y/n</td>
<td>y/n</td>
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<td>y/n</td>
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9.0 Efficacy Shells
**Table XX**  
*Shell Table for Primary Efficacy Endpoints (Overall)*

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=XX)</th>
<th>6 Months (n=XX)</th>
<th>Comparison of Baseline and 6 Month</th>
<th>12 Months (n=XX)</th>
<th>Comparison of Baseline and 12 Month</th>
<th>Comparison of 6 month and 12 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (lbs)</td>
<td>xx.x / xx.x</td>
<td>xx.x</td>
<td>p= x.xx</td>
<td>xx.x</td>
<td>p= x.xx</td>
<td>p= x.xx</td>
</tr>
<tr>
<td>Mean +/- SD</td>
<td>xx.x</td>
<td>xx.x</td>
<td></td>
<td>xx.x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>xx.x / xx.x</td>
<td>xx.x</td>
<td>p= x.xx</td>
<td>xx.x</td>
<td>p= x.xx</td>
<td>p= x.xx</td>
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<tr>
<td>Mean +/- SD</td>
<td>xx.x</td>
<td>xx.x</td>
<td></td>
<td>xx.x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% EWL</td>
<td>xx.x / xx.x</td>
<td>xx.x</td>
<td>p= x.xx</td>
<td>xx.x</td>
<td>p= x.xx</td>
<td>p= x.xx</td>
</tr>
<tr>
<td>Mean +/- SD</td>
<td>xx.x</td>
<td>xx.x</td>
<td></td>
<td>xx.x</td>
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<td></td>
</tr>
</tbody>
</table>

**Crude and Adjusted Values will be run**
Table XX

Shell Table for Primary Efficacy Endpoints (by Center)

<table>
<thead>
<tr>
<th>Center</th>
<th>Baseline (n=XX)</th>
<th>6 Months (n=XX)</th>
<th>12 Months (n=XX)</th>
<th>Comparison of Baseline and 6 Month</th>
<th>Comparison of Baseline and 12 Month</th>
<th>Comparison of 6 month and 12 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight (lbs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean +/- SD</td>
<td>xx.x / xx.x</td>
<td>xx.x /</td>
<td>p= x.xx</td>
<td>p= x.xx</td>
<td>p= x.xx</td>
</tr>
<tr>
<td></td>
<td>BMI (kg/m2)</td>
<td>xx.x / xx.x</td>
<td>xx.x /</td>
<td>p= x.xx</td>
<td>p= x.xx</td>
<td>p= x.xx</td>
</tr>
<tr>
<td></td>
<td>% EWL</td>
<td>xx.x / xx.x</td>
<td>xx.x /</td>
<td>p= x.xx</td>
<td>p= x.xx</td>
<td>p= x.xx</td>
</tr>
</tbody>
</table>

**Center A**

Weight (lbs)

Mean +/- SD

BMI (kg/m2)

Mean +/- SD

% EWL

Mean +/- SD

**Center B**

Weight (lbs)

Mean +/- SD

BMI (kg/m2)

Mean +/- SD

% EWL

Mean +/- SD
### Center C

**Weight (lbs)**
- Mean +/- SD: \( xx.x / xx.x / xx.x / p= x.xx \)

**BMI (kg/m2)**
- Mean +/- SD: \( xx.x / xx.x / xx.x / p= x.xx \)

**% EWL**
- Mean +/- SD: \( xx.x / xx.x / xx.x / p= x.xx \)

### Center D

**Weight (lbs)**
- Mean +/- SD: \( xx.x / xx.x / xx.x / p= x.xx \)

**BMI (kg/m2)**
- Mean +/- SD: \( xx.x / xx.x / xx.x / p= x.xx \)

**% EWL**
- Mean +/- SD: \( xx.x / xx.x / xx.x / p= x.xx \)

### Center E

**Weight (lbs)**
- Mean +/- SD: \( xx.x / xx.x / xx.x / p= x.xx \)

**BMI (kg/m2)**
- Mean +/- SD: \( xx.x / xx.x / xx.x / p= x.xx \)

**% EWL**
**Center F**

**Weight (lbs)**

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Center</th>
<th>Weight</th>
<th>BMI</th>
<th>%EWL</th>
<th>6 Month</th>
<th>BMI</th>
<th>%EWL</th>
<th>Weight</th>
<th>BMI</th>
<th>%EWL</th>
</tr>
</thead>
<tbody>
<tr>
<td>xxx001</td>
<td>xxx</td>
<td>xx.x</td>
<td>xx.x</td>
<td>kg/m2</td>
<td>xx.x</td>
<td>xx.x</td>
<td>kg/m2</td>
<td>xx.x</td>
<td>xx.x</td>
<td>kg/m2</td>
</tr>
<tr>
<td>xxx002</td>
<td>xxx</td>
<td>xx.x</td>
<td>xx.x</td>
<td>kg/m2</td>
<td>xx.x</td>
<td>xx.x</td>
<td>kg/m2</td>
<td>xx.x</td>
<td>xx.x</td>
<td>kg/m2</td>
</tr>
<tr>
<td>xxx003</td>
<td>xxx</td>
<td>xx.x</td>
<td>xx.x</td>
<td>kg/m2</td>
<td>xx.x</td>
<td>xx.x</td>
<td>kg/m2</td>
<td>xx.x</td>
<td>xx.x</td>
<td>kg/m2</td>
</tr>
</tbody>
</table>

**Listing XX**

**Shell Listing for Primary Efficacy Endpoints**
Title: Statistical Analysis Plan (SAP)

<table>
<thead>
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Title: Statistical Analysis Plan (SAP)

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10.0 **Safety Shells**
## Table XX

**Shell Table of Adverse Events (overall)**

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### Listing XXX

#### Shell Listing of Serious Adverse Events (Overall)

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5. Final statistical analysis plan V2.0
Title: Statistical Analysis Plan (SAP)

MAVERIC Study Specific Documents

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<td>NOVEMBER 2011</td>
<td>This document describes the statistical analysis plan for the VA KERATINO CYTE CARCINOMA CHEMOPREVENTION randomized clinical trial.</td>
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DOCUMENT/RECORD HISTORY:

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<th>DATE</th>
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<tr>
<td>11/09/2011</td>
<td>2.0</td>
<td>Revisions to Initial Version</td>
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AUTHORIZATION SIGNATURES

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1. Introduction
Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin, both keratinocyte carcinomas (KCs), account for a half of all cancers in the United States, and over 100,000 cases per year in the VA. Their standard treatment, excision of the lesion, costs the US health care system some $2.5 billion annually and about $100 million annually in the VA. There is no proven means to prevent KCs. An effective prevention strategy would dramatically change the way high risk patients are managed and could substantially reduce the costs of care. We hypothesize that topical 5-fluorouracil (5-FU) chemoprevention will prevent skin cancer and will be cost-saving. To test this we propose a randomized controlled trial of 5-FU compared to a vehicle control to the face and ears. In the study, 1500 veterans at high risk of skin cancer defined as at least 2 KCs in the prior 5 years, at least one of which was on the face or ears, will be randomized to 5-FU or a vehicle control cream, and followed 2 to 4 years. The endpoint will be the incidence of BCCs and SCCs on the face and ears. We will also assess the cost of care, quality of life, and side effects associated with treatment, and the prevalence and number of actinic keratoses, a skin cancer precursor and itself a cause of morbidity and cost. By targeting patients at high risk, the study focuses on high-cost patients for whom this treatment could both improve outcomes (cancers and quality of life) and reduce costs.

2. Study Objectives
   
   Primary Objectives:

   To determine the effect of topical 5-FU treatment (compared to a vehicle control treatment) on reducing surgeries for KC on the face and ears. This is to be determined in high-risk patients in a 4 year trial (2 years recruitment; average follow-up 3 years). Everyone in the trial will receive enhanced patient education and free sunscreen for the duration of the trial.

   Secondary Objectives:

   To evaluate the cost-effectiveness of this intervention, and effect of the 5-FU treatment on the incidence of surgery for BCC, on the incidence of surgery for SCC, on cryotherapy to the face and ears and prevalence of AKs, on quality of life, and on the frequency and severity of specific side-effects of the treatment.

STUDY OUTCOME MEASURES

A. Primary Outcome:
The primary outcome will be the time to diagnosis of the first KC on the face or ears for which surgery is performed. By requiring surgical treatment, we are focusing on the more consequential lesions associated with morbidity and cost for our primary outcome. It should be noted, however, that we expect approximately 91% of the KCs diagnosed in this study to be treated surgically (based on our VATTTC Trial experience), as this is the standard treatment. This outcome uses a time-to-event survival analysis comparing the hazard rates with the two treatments.

B. Secondary Outcomes

Secondary outcomes includes cost-effectiveness, measures of AK's, quality of life, side effects of treatment, lesion locations, and use of NSAIDS. Also, included are outcomes related to the primary outcome such as,

1. Time to occurrence of first BCC for which surgery is performed, and separately of first SCC for which surgery is performed
2. Number of BCCs, SCCs, and overall KCs requiring surgery per person-year of follow-up
3. Time to occurrence of first KC, BCC, and SCC for which surgery is not performed
4. Surgeries not for KC's

C. Investigational Plan

1. Both groups:

All participants will receive patient education about skin cancer, including images of typical early skin cancer lesions, and will be counseled on sun protection and the use of sunscreen. Sunscreen will be provided to the participants free of cost for the duration of the trial. All participants will also be given detailed instructions on how to apply the medication, and shown photographs of a patient with a moderate to severe reaction to 5-FU to illustrate a possible reaction to the study medication.

2. Intervention group:

The intervention group will have topical 5-FU 5% cream applied twice daily for 4 weeks to the face and ears, to be initiated immediately after randomization. The FDA-approved treatment for AKs is twice daily for 2-4 weeks (28 to 56 total doses), and for superficial BCC is 3-6 weeks twice daily (42 to 84 total doses). These two schedules overlap; for this study the treatment duration will be 4 weeks (56 doses). The 5-FU will
only be given once although multiple treatments might potentially be more effective. We expect to be able to detect effectiveness of a single treatment. There are currently no data on which to determine the optimal interval between 5-FU chemopreventive treatments.

We hypothesize that the 5-FU treatment will destroy KC precursors, and because of their slow progression will therefore have a prolonged effect on KC incidence, despite the short course of treatment. The ultimate use of this chemopreventive strategy will undoubtedly involve re-treatment. The data from this study will guide estimation of duration of effect of a single treatment and the appropriate length of a re-treatment interval (see XI.G.1.).

If the participant is unable to tolerate the twice daily 5-FU, they will discontinue the treatment and initiate “cool-down” treatment with triamcinolone 0.1% cream twice daily until the symptoms resolve. In these reactions, symptoms generally resolve within the first 3 days. Asymptomatic erythema typically resolves in about 2 weeks. At 3 weeks after stopping 5-FU, if and only if the participant has not received at least the minimum 2 week (28 dose) course, 5-FU treatment will be resumed on a once-daily basis to complete the 56 dose course. If this is not tolerated, the “cool-down” routine will be followed, but 5-FU will be stopped. It is commonly assumed that the inflammatory response indicates an adequate dose of the topical 5-FU has been received, in which case even those who stop early are likely to benefit from the chemopreventive effect of the experimental cream.

Clinical experience indicates the importance of counseling regarding possible reactions for the successful use of this agent. This counseling will be provided by the on site study nurse, who will talk with all participants at each visit and weekly by phone during the treatment. Study nurses will be trained for counseling prior to use and during use, and for appropriate handling of potential issues that may arise during and after treatment.

B. Assessment schedule

Baseline visit:
- Assess inclusion/exclusion criteria (10 mins)
- Review Informed Consent (15 mins)
- Randomization (5 mins)
- Perform complete skin examination (10 mins)
- Baseline Interview to obtain relevant history (30 mins)
- Quality of Life assessment (10 mins)
Title: Statistical Analysis Plan (SAP)

- Intervention overview (10 mins)

  Telephone interview by study nurse (5 min)
  - Weekly during intervention phase
  - Once every three months during follow up

  Brief follow-up visit at 2 and 4 weeks, and every two weeks thereafter if still on treatment
  - Brief face/ears only assessment by study nurse (5 mins)
  - Study nurse counseling and focused interview (15 mins)
  - QOL assessment (10 mins) at 4 weeks

  Follow up visits (every 6 months)
  - Complete skin examination (10 min)
  - Follow up interview (time since last visit) (15 min)
  - If a potential skin cancer is to be biopsied, digital photograph to document precise location; if a surgery has been performed on a KC that had not been photographed, the location will be photodocumented
  - QOL assessment at 12, 24, and 36 month visit (10 min)

In order to better illustrate the typical assessment schedule for participants in VA CSP 562, the following figures have been included for review.
Figure 1: Typical assessment schedule for a participant in VA CSP 562. Note: Assumes average follow-up time of 3 years as stated in protocol, and no cool down period.

Figure 2: Assessment schedule for a participant in VA CSP 562 who undergoes a cool down period after initiating treatment for 1 week. As per protocol, the treatment is restarted after a 3 week cool down on a reduced dose of once per day.
3.1. Overall Study Design and Plan

This trial will be a double-blind, randomized, 4-year, two-arm trial. The trial will test the null hypothesis that the two strategies do not differ with respect to the time-to-event outcome, the first diagnosis leading to surgical treatment of a pathologically confirmed KC lesion.

In terms of the alternative hypothesis we wish to show that:

The 5-FU-based field treatment strategy is effective in the prevention of surgery for a pathologically confirmed KC lesion.

The four-year study can be divided into two periods; namely, a 2-year start-up and enrollment period, a 2-year follow-up period in which patients are only followed. Hence, the length of follow-up time may vary from 2-4 years. Assuming a uniform rate of enrollment the average potential follow-up time will be 3 years.
3.2 Efficacy and Safety Variables

3.21. Efficacy endpoints

PRIMARY HYPOTHESIS

The primary outcome will be the time to diagnosis of the first KC on the face or ears for which surgery is performed. By requiring surgical treatment, we are focusing on the more consequential lesions associated with morbidity and cost for our primary outcome. It should be noted, however, that we expect approximately 91% of the KCs diagnosed in this study to be treated surgically (based on our VATT clinical experience), as this is the standard treatment. This outcome uses a time-to-event survival analysis comparing the hazard rates with the two treatments.

Since we are evaluating chemoprevention, the primary outcome is surgery for primary lesions, not recurrent lesions. Recurrent lesions are recognized by their occurrence in the scar from prior removal of the cancer. We understand that recurrent lesions occur when malignant cells remain after removal or destruction of a KC, and those cells are frequently deep in the skin and therefore less suitable for treatment with topically applied agents.

This endpoint will be ascertained either at the scheduled follow-up examinations or at examinations requested by the patient. At each study visit, the participant will be questioned about any skin cancers or surgeries. Any potential KCs designated for surgical intervention will be noted for later tracking on Form 10: KC Treatment, and the VA electronic record will be checked to ascertain or confirm the occurrence of the KC and the surgical procedure. For all participants in the trial, all pathology reports of biopsies from the skin of the face or ears will be reviewed at the chairman's office to determine the diagnosis of all lesions biopsied or otherwise surgically removed, and all of the histopathologic specimens surgically removed lesions will be reviewed by the central dermatopathologists. If a surgically excised lesion has the diagnosis of KC on initial biopsy, subsequent re-excision or Mohs surgery layers slides will not be sent for central review, since the lesion already has a centrally reviewed diagnosis of KC and hence qualifies as an endpoint. Skin cancers diagnosed outside of the VA, and associated surgeries, will be systematically sought in all participants to ensure that our outcome measure is complete. For any outside diagnosis or surgery, the medical record will be sought and reviewed. In the VATT clinical, 91% of KCs biopsied had a subsequent surgical treatment (some variety of excision or electrodesiccation and curettage), and diagnosis of KCs on the face and ears outside of the VA system represented only 1% of the total number of KCs on the face and ears during that 6-year trial.
We will use actual cancer occurrence for which surgery is performed, as opposed to occurrence of a precursor or intermediate marker, as the primary outcome because of the problems in the in reliability of diagnosis and counting precursor lesions36, their variable natural history, which includes a high probability of apparently spontaneous resolution, and a small probability of progression to invasive cancer2.5 The null hypothesis is that the two treatment groups (5-FU intervention and control therapy) do not differ in their time-to-event hazard rates. The alternative hypothesis is that intervention has a lower hazard rate than control therapy with a hazard ratio for control therapy compared to intervention exceeding 1.42.

NULL HYPOTHESIS
The null hypothesis is two-sided and thus we would reject the null hypothesis if the hazard ratio exceeded 1.42 or was less than 1/1.42 = 0.7, but only the former event would be deemed a success.

In summary, the design compares two treatments and the study outcome is the first diagnosis leading to surgical treatment of a pathologically confirmed KC lesion.

SECONDARY OUTCOMES

1. **Cost-effectiveness of the treatment strategy**: It is common for susceptible individuals to have multiple AKs and KCs. The cumulative resources devoted to their care and specifically the treatment costs are large (see I.B). The cost analysis will therefore look at potential short-term and long-term savings from this strategy in high-risk populations (see VII). KC treatments other than surgery, which are expected to be few, will also be included in this assessment.

2. **Time to occurrence of first BCC for which surgery is performed, and separately of first SCC for which surgery is performed**: The etiologic differences between BCC and SCC indicate that a chemopreventive intervention may have differential effects between the two histopathologic types of KC. As reviewed in Section I, there is substantial evidence that the proposed intervention will be effective for both histologic types. Since there are identifiable populations at greater risk for BCC, and others for SCC, delineating the value for each separately is worthwhile. We will also examine predictors of BCC and SCC occurrence.

3. **Number of BCCs, SCCs, and overall KCs requiring surgery per person-year of follow-up**: Because patients often will have multiple KCs, we will evaluate the number of BCCs, SCCs, and KCs per person-year of follow-up. This may show that the treatment reduces the overall numbers of KC over time.
4. **Time to occurrence of first KC, BCC, and SCC for which surgery is not performed.** This will allow us to determine any effect of the study intervention on a later decision to treat a skin cancer surgically, instead of by an alternative modality. The numbers not treated surgically are expected to be small (about 9% of KCs diagnosed), so only an (unexpected) large effect could be noted in this analysis.

5. **Measures of AKs:** We will also measure AKs because the morbidity and cost associated with these skin lesions is large (see section I). Also, the intervention tested has known efficacy against AKs, so reduced AKs and reduced need for treatment of AKs may be important benefits of the regimen. We will count AKs greater than 5 mm in diameter, a reliable measure\(^{37}\). We will also count and measure cryotherapeutic treatments as an outcome; this is the standard treatment for AKs. Cryotherapy treatments will be a component of the cost-effectiveness analysis. Any treatments for AKs other than cryotherapy will also be measured.

6. **Surgeries not for KC:** We will examine whether there is a difference between groups in surgery on the face and ears for lesions other than KC. This will also be a component of the overall cost-effectiveness analysis.

7. **Side-effects of treatment:** Specific indices of chemopreventive treatment side-effects (especially pain, itch, sores/crusts, and erythema) will be ascertained. The measurement will include questions regarding the presence and degree of symptoms such as pain/burning and pruritus of the face and ears as well as erythema.

8. **Quality of life:** Skin cancer can cause substantial anxiety, disfigurement, and other morbidity. For quality of life, we will use the Skindex (a published, validated, widely used quality of life instrument for skin disease)\(^{38}\). This is a brief questionnaire completed by the participant.

Morbidity from KC may include both morbidity from the cancer and from the treatments. When cancer is diagnosed, treatment of AKs may result in short-term pain and long-term depigmentation that may be disfiguring. Hence the quality of life measure reflects morbidity due to the skin cancers, morbidity due to AKs, morbidity due to their treatment, and morbidity due to the chemoprevention interventions themselves.

9. **Exploratory analysis of endpoint location:** We will review photographs of endpoint lesions to ascertain any particular sub-areas on the face and ears at which the chemopreventive treatment may have been more or less effective.
10. **Nonsteroidal anti-inflammatory medications (NSAIDs):** We will assess use of NSAIDs (OTC and prescribed) to evaluate their relation to KC risk, since that association has been suggested but is controversial\textsuperscript{45,46}.

**Study procedures related to unblinding the study**

During the study, the accumulative study data will encode the two treatment strategies as ‘A’ and ‘B’. All analyses by treatment will be blind; that is, the treatments will only be identified as ‘A’ and ‘B’. When the study ends and subsequently the final dataset is locked, then the treatments will be unblinded so that the analysts and the principal investigator can write the primary paper. In the unusual circumstance that the DMC requests the data be unblinded before the study ends, the only MAVERIC staff members to be unblinded will be the 1) statistician responsible for the primary analysis, and 2) as few other persons needed to interpret the results of analyses requested by the DMC. Staff who directly deal with the day-to-day data will not be unblinded. The director of MAVERIC will determine whom to unblind as appropriate to the specific DMC request. A record to file will list those persons and the date they were unblinded.

3.2.2 **Safety Variables**

The safety variables are the serious adverse events; namely death, hospitalization, other SAE's. In addition, safety outcomes include all adverse events related and unrelated to treatment.

4. **Statistical Methods**

4.1 **Study Subjects**

4.1.1 **Disposition of Subjects**

The number of subjects screened, enrolled, and completing the study will be presented overall and by center subdivided by demographic categories (i.e., gender, race, etc.)

Reasons for the early termination of subjects as noted on the CRF will be summarized. Subjects that are lost to follow-up will be summarized as one category.

The following listings will be provided:
Title: Statistical Analysis Plan (SAP)

- A by-subject listing of completion/termination details
- A by-subject listing of protocol violations and deviations

4.1.2 Analysis Populations

All enrolled subjects will be included in the subject listings (by study ID number).

All eligible subjects who gave consent will not be included in the analysis. Only subjects who begin to receive treatment will be included in the safety (safety population) and efficacy (efficacy population) analyses.

4.2 Demographics and Baseline Characteristics

4.2.1 Demographics

Demographic details (e.g., age, sex, ethnicity, race, marital status, and smoking status) will be summarized overall and by center.

4.2.2 Medical History and Comorbidities

The pertinent medical histories (i.e., comorbidities), and history of AKs and skin cancer will be summarized overall and by center. (frequencies and percentages will be given).

4.3 General Considerations

In general the number of observations, mean, median, standard deviation, minimum, and maximum will be calculated for continuous variables. The number of decimals place will be as follows: minimum and maximum to the same number of decimal places as present in the raw data, mean and median to plus one decimal place, standard deviation to plus two decimal places. Frequencies and percentages will be calculated for categorical data.

Baseline is defined as the baseline assessment visit.

Missing endpoint data will not be imputed. Missing covariate data will be imputed in selected circumstances as described below.

All planned analyses for the final clinical study report will be performed using a two-sided nominal significance level of 0.05; however, comparisons less than 0.10 will also be discussed as being marginally significant.
4.4 Efficacy Evaluation

4.4.1 Primary Efficacy Analysis

The study will enroll a total of 1000 patients, 500 of whom will receive the topical 5-FU-based treatment, and 500 of whom will receive the control treatment. We will enroll 500 patients per year for two years to accrue 100 patients per site at 10 VA medical centers.

The outcome measure distinguishes between surgical excisions of a pathologically confirmed KC lesion (either BCC or SCC lesion) and the rare excisions that result in any other diagnosis. Because chemoprevention may have no effect on other lesions, only KC lesions will be counted for the primary outcome.

The primary outcome measure is:

The time after enrollment in the study until the first diagnosis leading to surgical treatment of a pathologically confirmed KC lesion.

In terms of the alternative hypothesis we wish to show that:

The 5-FU-based field treatment strategy is effective in the prevention of surgery for a pathologically confirmed KC lesion.

A. The Primary Outcome:

The null hypothesis is that the two treatment groups (5-FU intervention and control therapy) do not differ in their time-to-event hazard rates. The alternative hypothesis is that intervention has a lower hazard rate than control therapy with a hazard ratio for control therapy compared to intervention exceeding 1.42.

This four-year study will enroll patients for 2 years so that the last patient enrolled will potentially have up to 2 years of follow-up. The first patient enrolled will potentially have up to 4 years of follow-up. On average, patients will potentially have approximately 3 years of follow-up. Thus, the power calculations are based on estimates of a surgically treated diagnosis of KC within 3 years.

Based on the VATTC study we expect the 3-year rate of surgical excision of a pathologically confirmed KC lesion will be 44%. This is a VATTC incidence rate as opposed to a surgery rate, but these will negligibly differ.

We have chosen a 3-year of 42% for the outcome, surgical excision of a pathologically confirmed KC lesion. We make this 2% reduction for several reasons. First, a rare patient who developed both a SCC and a BCC at the same
time will only be counted once. Second, in the proposed study, the 3-year incidence rate for KC may be slightly reduced because of differences between the old VATTC protocol and the proposed protocol. In the proposed trial physicians will adhere to their internal policies and tend to systematically remove many of AK's with cryotherapy and thereby may lower the 3-year KC rates. In the VATTC trial, centers were asked to take a watchful waiting policy on most AK's, but tended to follow their own internal policies on this matter. Third, for the proposed trial we will exclude patients who had 5-FU treatment during the 3 years prior to enrollment, and we speculate that these patients may be at higher risk for KC's than the eligible patients. To account for these three factors we assume that the KC rate for the proposed trial will be 95% of the VATCC rates.

Under the null hypothesis:

The three-year KC surgery rate will be 42%

Under the alternative hypothesis for patients treated with 5-FU:

The three-year KC surgery rate will be 32%

The reductions attributed to treatment may be viewed in several ways. The absolute reduction from 42% to 32% is 10%, the relative reduction is \((42 - 32)/42 = 24\%\), and the hazard ratio (control hazard rate/treatment hazard rate) of 1.42 midway between the simple odds ratio, \(42(100-32)/(32(100 - 42)) = 1.54\) and the risk ratio \(42/32 = 1.31\).

Sample Size and Statistical Power Considerations

The results for the KC primary outcome measure, time until first SCC diagnosis, will be analyzed by means of the two-sided log-rank test to detect either a hazards ratio that exceeds 1.42 or is less than 1/1.42 = 0.74. The test will have a two-sided 4.8% type I error. (When added to the interim analysis that has a 0.2% Type I error, the overall type I error is 5%). The test has 90% power to detect a ratio of hazards of 1.36 or larger or 0.70 or less with a total of 1000 patients, 500 per study arm. This assumes that 8% of the patients either die or are lost to follow-up while on-study before a SCC diagnosis can be observed. The power for the log-rank test was computed using Schoenfeld's formula (see equation 18.10 in Buyse, Staquet and Sylvester, 1984).

Interim Analysis
We will perform one interim analyses when the first 500 patients (250 in each study arm) enrolled have completed two years of follow-up. Assuming a uniform rate of enrollment over time this interim analysis should take place at the end of year 3. With an 8% loss-to-follow-up rate each study arm will have 210 evaluable patients.

The one interim analysis carried out when the 500\textsuperscript{th} patient completes two years of follow-up has a small effect on overall type I error. The interim analysis has a Type I error of 0.2%. The interim analysis is two-sided, but the interim null hypothesis will only be rejected if the hazard ratio exceeds 2.39. If the hazard ratio is less than $1/2.39 = 0.42$ then trial will be stopped for futility.

After 3 years the first patient entered will potentially have 3 years of follow-up and the last patient entered will potentially have 1 year of follow. Thus, the average potential follow-up will be two years. If we expect a 44% KC rate at three years then under the exponential model we would expect a 32% KC rate at two years.

Under the interim analysis null hypothesis:

The two-year KC rate will be 32%

Under the interim alternative hypothesis for patients treated with 5-FU:

The three-year KC rate will be 16%

The reductions attributed to treatment may be viewed in several ways. The absolute reduction from 32% to 16% is 16%, the relative reduction is $(32 - 16)/32 = 50\%$, and the hazard ratio (control hazard rate/treatment hazard rate) is 2.39.

We considered earlier times for interim analyses, but rejected this idea because sample sizes on the order of 150 per study arm only have modest power to detect very large effects.

For both the interim analysis and the primary analysis we considered the possibility that the effect of 5-FU merely delays the clinical emergence of a KC by a short period, such as 6 months. Then a wide gap between control and treatment arms, due to lower incidence in the treatment arm, might rapidly narrow with more follow-up. Indeed, this possibility led us to propose to monitor VA electronic records and passively follow patients after the four-year study ends to detect such narrowing. Finally, compared to other types of cancer KC's are seldom fatal, so that the evaluation of costs to the VA and patient morbidity assume greater importance. We expect that to gather the data for these evaluations would prolong the trial past the early stopping date.
Data Analysis Plan

The primary outcome hypothesis will be tested using a two-sided log-rank test to compare the hazard rate for one treatment group to that for another treatment group. A significant difference showing that the intervention strategy compared to the control decreases the hazard of surgery for pathologically confirmed KC will be regarded a positive result, whereas a result that shows intervention does not significantly differ from or, in fact, significantly increases the hazard rate will be regarded as a negative result. We will report the hazard rates, their ratio and the 95% confidence interval about the ratio.

The SAS code for this analysis is:

```sas
proc phreg data = c562.final_date;
model followup*primary(0) = txb / rl;
title "Basic model - Cox model";
```

In this code the dataset is dated to coincide with the data freeze date for DMC meeting. 'Followup' refers to time until surgery. Primary has two values: 0-censored and 1-surgery.

This will be followed by further refined analyses, using multiple linear Cox proportional hazards regression modeling, to take account of the effects of baseline covariates on the primary outcome measure. Covariates will include demographic and clinical factors (age, sex, smoking status, education, number of AK’s, history of BCC, of SCC, or both).

The regression modeling we shall employ will include a model with treatment by covariate terms to explore the possibilities of treatment by covariate effects (that is, exploration of potential subgroup effects). We will test the proportional hazards assumption by including a time-treatment interaction term in the model. We will use graphic methods to study goodness-of-fit as described in section VII.3.1 of the text 'Statistical Models based on Counting Processes' (Anderson K, Borgan O, Gill RD, and Keiding N, Springer-Verlag New York 1991).

**Extended Follow-Up**

The four-year study can be divided into two periods; namely, a 2-year start-up and enrollment period, a 2-year follow-up period in which patients are only followed. Hence, the length of follow-up time may vary from 2-4 years. Assuming a uniform rate of enrollment the average potential follow-up time will be 3 years.

The power calculations account for both the varying amount of follow-up time and for the censoring of outcomes. Varying follow-up time and the length of the recruitment
period have negligible effects on power. We have assumed an 8% rate of lost-to-follow-up combining the on-study death rate with the study lost-to-follow-up rate. Hence, the statistical power calculation is based on the 920 evaluable patients among the total of 1000 enrolled.

When the study ends after 4 years we will continue for one year to follow patients who have not had a new KC surgery by tracking the medical procedures they have as reported in the VA Austin database. We will look for an excess of KC surgical events in the 5-FU treatment arm indicative of events delayed by treatment as opposed to prevented by treatment.

4.4.2 Secondary Efficacy Analysis

Secondary analyses are of several types; analyses directly related to the primary hypothesis of BCC and SCC surgical endpoints, quality of life as measured by the Skindex instrument, multiplicity of AK’s, and cost analyses. Cost analyses are described in section VII.

Time to surgery for a new BCC and for a new SCC:

In analyses directly related to the primary hypothesis, we will disaggregate KC into its components BCC and SCC. Then we will compare the treatments with respect to each of the two separate outcomes of the time to a diagnosis leading to surgery for a new SCC and time to a diagnosis leading to surgery for a new BCC using the analogous time-to-response analysis delineated for the primary analysis. For this secondary outcome each of the two parallel null hypotheses is that the two treatment groups (intervention and control therapy) do not differ in their time-to-event hazard rates. As in the primary analysis, we will begin with the two-sided log-rank test for each of the two outcome measures, time until the first BCC diagnosis leading to surgical treatment of a pathologically confirmed SCC lesion and time until the first BCC diagnosis leading to surgical treatment of a pathologically confirmed BCC lesion.

We will carry out two additional time-to-event analyses of the aggregated KC outcome. We will apply the log-rank test to the data obtained from the extended follow-up beyond 4 years as in the primary analysis. This analysis will be done on both the final data set when the trial ends and on the extended follow-up data set. For each of these analyses we will report the hazard rates, their ratio and the 95% confidence interval about the ratio. This will be followed by further refined analyses, using multiple linear Cox proportional hazards regression modeling, to take account of the effects of baseline covariates on the primary outcome measure. Covariates will include demographic and
clinical factors (age, sex, smoking status, education, number of AK’s, and history of BCC, of SCC, or both. The regression modeling we shall employ will include a model with treatment by covariate terms to explore the possibilities of treatment by covariate effects (that is, exploration of potential subgroup effects).

These secondary analyses are exploratory in nature and thus we have not assigned it a level of power. Extensive exploratory analyses will address the issue of the optimal time interval between applications of 5-FU therapy. Assuming that one 5-FU treatment reduces the hazard of surgical outcomes, we will separately study the disease endpoints of BCC, SCC, and KC to determine the shape of the hazard rate over time for the 5-FU treated and control patients. The objective will be to estimate the hazard rate for a new BCC, SCC, or KC in the treated and untreated groups. We will use an extension of the proportional hazards model, specifically with a Weibull frailty model that provides an explicit model for the hazard rate. In particular, we will test whether the hazard rate for patients treated with 5-FU remains flat or rises over time. This would address the question of whether 5-FU treatment delays the incidence of new KC’s. Relative to the hazard rate among controls and to a flat hazard rate, the pattern of a rising hazard rate over time would indicate that 5-FU delayed KC incidence. If 5-FU is effective then the pattern of a flat hazard rate over time would indicate destruction of a proportion of KC’s but not delay.

Quality of Life:
We will compare the treatments with respect to the change in the Skindex score after one year and after two years. The change after one-year is the difference between the one-year score and the baseline score. The change after two years is the difference between the two-year score and the baseline score. Regarding these changes as continuous outcomes, we will use Student’s t-test to compare the treatments. Controlling for the covariates listed above we will carry out a linear regression analysis with treatment as the major factor. Confirmatory analysis will be done using combining the one-year, two-year, and three-year change scores into a repeated measures regression analysis. This analysis will treat the factor subject as a random effect and explore the possibility of different sizes of effect within each follow-up year.

Burden of Actinic Keratoses:
We will evaluate the effect of study treatment on the burden of actinic keratoses on the face and ears, as assessed by counts of large lesions, >= 5 mm in diameter. For the analyses of counts and for the number of spot treatments we will fix the follow period at two years and carry out a simple Poisson regression comparing the treatments and a more complex Poisson regression comparing the treatments and controlling for covariates. For the analyses of estimates of skin area affected (a continuous outcome) we will fix the follow period at two years and carry out a Student’s t-test comparing the
treatments and a more complex linear regression comparing the treatments and controlling for covariates. To confirm this analysis we will collapse the Poisson counts into ordinal categories; none, 1-3, 4-10, 10 or more. We will rerun the analysis using polychotomous logistic regression. For each of the proposed analyses viewing baseline and each follow-up year as repeated measures we will also analyze the data with subject as a random effect using the SAS procedure NLMIXED.

4.4.3 Cost analyses

Cost-effectiveness of the treatment strategy: It is common for susceptible individuals to have multiple AKs and KCs. The cumulative resources devoted to their care and specifically the treatment costs are large. The cost analysis will therefore look at potential short-term and long-term savings from this strategy in high-risk populations (see VII). KC treatments other than surgery, which are expected to be few, will also be included in this assessment.

Design Considerations for the Economic Analysis:

There are two components of the proposed economic analysis. First, we will conduct a cost-effectiveness analysis from both a VA and a societal perspective. Second, we will conduct a business impact, or cash-flow analysis from a VA perspective. The purpose of this second analysis will be to provide VA managers with the information that they need to accurately determine the financial impacts of adopting the study protocol as standard therapy. Both of these analyses are conditional on the main outcome of the study being an effective intervention. If the intervention doesn’t work, the economic analyses are moot, as the intervention will not be clinically adopted.

Skin cancer is a condition for which the treatment can be clearly separated from the treatment of other conditions. Thus, this study will not consider other health care costs; we will assume that the randomization equalizes these across the two study arms. The one exception to this is if a skin cancer metastasizes to another site. The costs and utilization associated with the treatment of metastatic cancers will be considered, conditional on site investigator verification that the metastatic cancer is related to BCC or SCC.

Preliminary calculations based on the effect sizes that the study is powered on project a cost savings associated with the intervention. Further, these cost savings will persist for a wide range of assumptions about the costs of therapy and the effectiveness of the intervention. Thus, there will only be conditional collection of health utilities information. If the initial analysis at the end of the trial show that we need to value the relevant health state utilities, we will submit a supplemental proposal to CSSMRB for the collection of
health utilities. Study information from the skin cancer-specific quality of life measures collected during the study, will be used to determine the health states that need to be valued. Community ratings will be obtained for these health states. Since study subjects are not required for this method of utility assignment, the collection of the utility data can be deferred without jeopardy to the proposed analysis.

Sources of Cost and Utilization Data

VA costs will be captured from the VA Decision Support System (DSS) National Data Extracts (NDEs). DSS is a comprehensive, activity-based hospital accounting system that VA uses to track its costs. Summary extracts are made from this system that tract inpatient, outpatient, and pharmacy costs. These data are extracted and converted to SAS datasets at the VA Austin Automation Center (ACC) on an annual basis. They are usually available in February of each year.

Encounter data with ICD-9-CM codes for all encounters, and CPT codes for outpatient encounters are also available from the National Patient Data Base SE file at the ACC. These data will allow centralized tracking of all VA patient care encounters.

At many VA facilities at least some of the skin cancer-related care (especially Mohs surgery) is provided as contract care. To ensure complete data for this care, each site will be asked to identify the types of care that they routinely provide under contract or fee-basis care. Study forms will be used to capture the CPT codes for all fee-basis and contract care. While there are centralized databases of fee basis care, these data have never been carefully assessed for completeness. Further, starting in FY 2007, all fee-basis and contract care is supposed to be captured by DSS. Once the FY 2007 DSS extracts are available in early 2008, HERC will compare the data reported on the study forms with the fee-basis and contract care reported in DSS. If the DSS is found to accurately capture these data, use of the study forms for contract and fee-basis care will be discontinued.

Non-VA Health Care

Prior experience from CSP #402 found that 99% of the KC-related care was VA provided. Thus, while patients will be asked to self-report their use of related care obtained from a non-VA provider, the impact of errors of patient self-reporting will be minor. At enrollment, patients will be asked to bring copies of the billing statements for any non-VA skin cancer-related care to each subsequent follow-up visit. At each follow-up visit, the site coordinator will ask the patient if any non-VA skin cancer-related care was received since the last visit. If the patients does not provide copies of the billing statements, the site coordinator will use a study form to determine what non-VA care was provided. Fortunately, there are only a few types of patient care encounters that
are relevant care. Thus, the study form will list each of the types of service. VA averages for these types of encounters will be used to assign costs to these encounter types. Patients will also be asked for the date of service. These self-reported uses of non-VA care will be cross-checked with the VA databases, especially the fee-basis files, to prevent double counting.

Patients will also be asked at enrollment if they are currently enrolled in Medicare (median age for CSP #402 was 71). If they are not currently enrolled in Medicare, they will be asked if they expect to enroll in Medicare during the study period. The consent form will include permission to access Medicare records. A finder file of all study patients will be submitted to VIREC, which is the VA repository of the Medicare data for users of VA care. These Medicare data will be used as a further check for study relevant non-VA health care utilization. Given the lag in the linking of the Medicare data to VA users, the Medicare data may not be available for the last year of the study at the time of analysis. But, the Medicare data will provide data for earlier years of follow-up and allow the assessment of the completeness of the patient self-report of use of non-VA care.

Assumptions for Preliminary Cost Analysis:

The VA cost of 5-FU was obtained from the April 2007 list of current VA drug prices maintained by the VA Pharmacy Benefits Management (PBM) group. It was assumed that two 40g tubes of 5-FU would be sufficient for each course of chemo-preventive therapy. The April 2007 cost of a 40g tube of 5-FU was $80.42, yielding a per treatment cost of $160.84. The CPT codes were identified for Mohs facial surgery, and the 2005 VA frequency of use of these codes identify their relative use in VA. Using 2006 Medicare RVUs, conversion factors, and APC facility payment rates, we calculated an average cost of $830. This cost decreases to $715 if the surgery is done in conjunction with one of the more expensive types of reconstructive surgeries due to the facility payment methodologies for ambulatory surgery.

To estimate the VA costs for reconstructive procedures, we examine the “repair” codes recorded in VA encounters where Mohs surgery was performed. We used the weighted average of these payments, with adjustments for the Medicare facility payment methodology to obtain a weighted average VA cost for Mohs surgery and reconstruction of $1573.

Based on the information from CSP 402 and a search of centralized VA data, we know that the patients who will be enrolled in this trial have a high incidence of AK, which will almost always be treated with cryosurgery. Again, we used the actual VA use of CPT codes to calculate a weighted average cost for a cryosurgery of $138.
While it is possible that the intervention will reduce other VA costs of care, no other potential savings were included for this preliminary analysis. We acknowledge that there will probably be some added costs of the intervention for following up with patients by telephone during the intervention period. These will be captured during the actual analysis, with care to make sure that they exclude the additional visits/contacts that were part of the research project, not actual patient care. The cost of the initial visit at which the 5-FU is dispensed will not be included as this would be done at a regularly scheduled annual encounter for these high-risk patients.

From the power calculation of this trial, we are conservatively projecting an absolute reduction of 11% in the number of KC that will require surgical treatment. For the base analysis, we also assumed that on average, 0.75 cryotherapy treatments per patient would be averted. This is a fairly conservative assumption, given that 5-FU is known to be an effective therapy for AK and the study patients average more than 1 AK per year, with an average follow-up of 3 years. These assumptions result in a net savings of $116.

We also tested the sensitivity of these assumptions. If no reductions in AK therapy are assumed, the net savings, due solely to the reduction in Mohs surgery is $13. With the 0.75 cryotherapy treatments averted per patient for the treatment of AK, there are net savings as long as the reduction in the need for surgical treatment for facial KC is greater than 3.6%. Net savings also remain with 0.5 cryosurgeries averted per patient as long as the reduction in surgical treatment for facial KC is at least 5.8%.

The cost-effectiveness analysis will be an intent-to-treat analysis, using an incremental cost-effectiveness ratio, and a societal perspective. All costs and benefits will be discounted at a 3% rate. We will monitor the development of the emerging concept of presenting the results in terms of a net health benefit, and will consider this method as an alternative for presenting the results. Essentially, we are acknowledging that this new method could change the consensus on how to report cost-effectiveness studies, and that we will be sensitive to this possibility.

Because this is a VA trial, the cost-effectiveness analysis will be repeated from a VA perspective. This will be done by revising the final analysis to only include the costs directly incurred by VA. This will have no affect on the QALY expressed benefit to the study subjects.

Given the strong prior that the study results will show the intervention to be effective and have a net cost savings (i.e. strong dominance), the utility/QALY assessment will be conditional. The changes in net health utilities associated with the different therapies in this study are likely to be relatively small. Standard indirect utility instruments such as the HUI and the EQ-5D are unlikely to be sensitive enough to detect these changes.
The study will regularly collect data using disease-specific quality of life instruments. These instruments will provide sufficient information to allow the characterization of the health states that are most relevant to the study. If the initial analysis at study close-out shows that the net costs of the intervention may be positive, then supplemental funding will be requested to allow the outcomes from the disease-specific quality of life instruments to be mapped to utilities. These utilities will be assigned using a community sample of healthy adults. The study economist has prior experience with this method; he worked with colleagues at Stanford University to obtain community-rated utilities for the Activities of Daily Living scores that were used to measure patient functioning for Geriatric Evaluation and Management patients in CSP #006. Application of this method will allow utilities to be assigned to the disease-specific quality of life measures that will be recorded for study subjects at regular intervals. The advantage of this approach is that it avoids the significant expense of assigning utilities to health states unless it is necessary for the completion of the analysis.

We also acknowledge the possibility that the interventions have differential effects on patient quality of life that could be the opposite of our expectations. The intervention will treat all patients to prevent the occurrence of KC in some patients (the intervention will also prevent the occurrence of AK in a larger fraction of patients). Thus, all of the intervention patients will experience some disutility associated with the treatment, while only a subset will receive the utility benefits of averted KC or AK. While the hypothesis is that the intervention arm will result in net higher disease-specific quality of life ratings, we will examine the results to confirm this. If the results of the disease-specific quality of life ratings don’t clearly show a net benefit to the intervention arm, this would also trigger the collection of utilities data from a community sample.

Cash-Flow Analysis:

The VA is operated on a fixed global budget. VA managers must make decisions on where and how to allocate fixed resources. While traditional clinical trials results can make a compelling case about the effectiveness of an intervention, they don’t provide all of the information that managers need to implement the adoption of new technologies or treatments. Even if this study has the expected outcome of a net savings attributable to the intervention, this alone will not provide sufficient information for VA managers. This is because the study intervention requires an up front investment in chemo-preventive therapy. The up front costs will not be fully recouped in the first year. To allow VA managers to adequately plan for the adoption of chemo-preventive 5-FU therapy, we also plan to use the study data to calculate the expected cash flow affects of implementing the study intervention. We will use the actual utilization of care for patients in the control arm of the study to project when the averted treatments would have occurred, in terms of months since initiation of 5-FU treatment. These will be summarized on a quarterly basis, and compared with the cost of 5-FU therapy.
HERC has planned to include this type of cash-flow analysis in other CSP trials that are already in progress. The intent is to work with various VA leadership organizations to help disseminate this information. If this trials shows the intervention is effective, we will build on these previous management dissemination efforts. The purpose of this type of analysis is to make the results as useful as possible for VA managers. Feedback from this type of effort for other CSP trials will be incorporated into the exact dissemination plan.

4.5 Safety Evaluation

All safety summaries will be based on the Safety Population described in Section 4.1.2 "Analysis Populations."

4.5.1 Mortality

The frequency and proportion of all deaths will be presented overall and by center.

A by-subject listing will be provided.

4.5.2 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 9.0) coding dictionary.

All AE summaries will be based upon the number of subjects reporting AEs and not the number of events reported. Adverse events (AEs) will be tabulated (i.e., those events that were not present at the baseline evaluation or worsened in severity following the start of treatment). Any AEs starting after study completion or withdrawal will not be tabulated.

If the AE start date is not a complete date, the following rules will be applied to determine whether the AE will be tabulated or not.

If the start date is completely missing:
  - The AE will be tabulated unless the AE stop date is less than the baseline date.

If the day part of the AE start date is missing, use the following algorithm:
  - If the month and year of the start date are later than or equal to the month and year of the surgery, then the AE will be tabulated. If the month and year of the stop date are earlier than the month and year of the surgery, then the event will be assumed to not be tabulated.
If the day and month of the start date are missing, use the following algorithm:

- If the year of the start date is later than or equal to year of the surgery, then the AE will be tabulated. If the year of the stop date is earlier than the year of the surgery, then the event will not be tabulated.

The number and percentage of subjects with AEs through the end of the study (analysis period) will be summarized by system organ class and preferred term overall.

Summaries of AEs by intensity and relation to study device will be presented by system organ class and preferred term overall. For each subject and each AE, the worst intensity/relation recorded will be attributed and used in the intensity/relation summaries. If intensity/relation is missing, the intensity/relation will be queried by data management.

The number and percentage of subjects with serious adverse events (SAE) through the end of the study (or analysis period) will be summarized by system organ class and preferred term overall.

A by-subject listing of all AEs will be provided.

A by-subject listing of all serious AEs will be provided.

4.6 Determination of Sample Size for the Primary Hypothesis

The results for the KC primary outcome measure, time until first SCC diagnosis, will be analyzed by means of the two-sided log-rank test to detect either a hazards ratio that exceeds 1.42 or is less than 1/1.42 = 0.74. The test will have a two-sided 4.8% type I error. (When added to the interim analysis that has a 0.2% Type I error, the overall type I error is 5%). The test has 90% power to detect a ratio of hazards of 1.36 or larger or 0.70 or less with a total of 1000 patients, 500 per study arm. This assumes that 8% of the patients either die or are lost to follow-up while on-study before a SCC diagnosis can be observed. The power for the log-rank test was computed using Schoenfeld’s formula (see equation 18.10 in Buyse, Staquet and Sylvester, 1984).

4.7 Missing Values Primary Analysis

Dropouts will be included in the primary analysis assuming random censoring but sensitivity analyses will address their potential that non-random censoring patterns
biased the results. Imputation of final outcomes requires questionable assumptions about treatment effects. We will consider a range of such assumptions in the confirmatory analyses. The confirmatory secondary analysis including the dropout data censored at the appropriate study visit will also be done to assess potential bias associated with the complete case analysis.

A covariate adjusted primary analysis will be done in order to either confirm or not confirm the primary analysis that has no covariates. In either case, the confirmatory analysis will indicate the degree of bias in the complete case analysis.

Practical measures will be taken to minimize missing values and losses to follow-up. One prominent conjecture about patients who drop out is that they tend to have poor outcomes. This clearly would violate the assumption of missing-at-random. Multiplicity

There will be no corrections done for multiple comparisons in this descriptive study.

4.8 Interim Analyses
We will perform one interim analyses when the first 500 patients (250 in each study arm) enrolled have completed two years of follow-up. Assuming a uniform rate of enrollment over time this interim analysis should take place at the end of year 3. With an 8% loss-to-follow-up rate each study arm will have 210 evaluable patients.

The one interim analysis carried out when the 500th patient completes two years of follow-up has a small effect on overall type I error. The interim analysis has a Type I error of 0.2%. The interim analysis is two-sided, but the interim null hypothesis will only be rejected if the hazard ratio exceeds 2.39. If the hazard ratio is less than 1/2.39 = 0.42 then trial will be stopped for futility.

After 3 years the first patient entered will potentially have 3 years of follow-up and the last patient entered will potentially have 1 year of follow. Thus, the average potential follow-up will be two years. If we expect a 44% KC rate at three years then under the exponential model we would expect a 32% KC rate at two years.

Under the interim analysis null hypothesis:

The two-year KC rate will be 32%

Under the interim alternative hypothesis for patients treated with 5-FU:

The three-year KC rate will be 16%
The reductions attributed to treatment may be viewed in several ways. The absolute reduction from 32% to 16% is 16%, the relative reduction is \((32 - 16)/32 = 50\%\), and the hazard ratio (control hazard rate/treatment hazard rate) is 2.39.

We considered earlier times for interim analyses, but rejected this idea because sample sizes on the order of 150 per study arm only have modest power to detect very large effects.

For both the interim analysis and the primary analysis we considered the possibility that the effect of 5-FU merely delays the clinical emergence of a KC by a short period, such as 6 months. Then a wide gap between control and treatment arms, due to lower incidence in the treatment arm, might rapidly narrow with more follow-up. Indeed, this possibility led us to propose to monitor VA electronic records and passively follow patients after the four-year study ends to detect such narrowing. Finally, compared to other types of cancer KC’s are seldom fatal, so that the evaluation of costs to the VA and patient morbidity assume greater importance. We expect that to gather the data for these evaluations would prolong the trial past the early stopping date.

4.9 Data Monitoring Committee
Data and study progress will be monitored by the study executive committee and by the study steering committee. The Data Monitoring Committee will review the study progress and safety on at least an annual basis with additional meetings and communications as needed.

5.0 Reporting Output
All outputs will be produced using SAS Version 9.1 or a later version (if available at MAVERIC). The REPORT procedure will be used to produce all tables and listings whenever possible. The GPlot and/or GCHART procedure will be used to produce all figures whenever possible. All statistical appendices (supportive SAS output) will be output directly from the appropriate SAS procedure.

All tables, listings, and statistical appendices will be produced to landscape orientation and will be incorporated into a Word 2003 document (margins: top 1.5”, left, right and bottom 1”) using Courier New 9pt font.

Tables, listings, and figures will be arranged in the order that they appear in the textual sections of this analysis plan, i.e., disposition first, followed by baseline summaries, efficacy summaries, and safety summaries.
Title: Statistical Analysis Plan (SAP)

All recorded data will be listed following the order and structure of the CRF. In addition, selected derived data used in the analyses will be listed. The listings will include all enrolled subjects (with data relevant to the particular listing) and will be ordered by center, subject, and visit.

6.0 Lists of Tables, Figures and Listings

A. Subject Disposition
   • Table A1. Recruitment, by Site
   • Listing A1. Protocol Deviations
   • Listing A2. Enrollment Waivers
   • Listing A3. Termination of Study Protocol
   • Tables A2. Form Completion Status
     • a. Baseline Forms Completion, Overall
     • b. Follow-up Forms Completion, Overall
     • c. Baseline Forms Completion, by Site
     • d. Follow-up Forms Completion, by Site

Baseline Characteristics
   • Table B1. Demographic Characteristics
   • Table B2. Lifetime Occupational Sun Exposure and Sensitivity History
   • Tables B3. Baseline Medical History
     • a. Baseline Medical History
     • b. Baseline Medical History: Concomitant Medication
   • Table B4. Skin Disease History at Baseline
   • Table B5. Previous Skin Cancer Pathology
   • Table B6. Count of Actinic Keratoses, Full Body Exam
   • Table B7. Study Medication Use
   • Table B8. Symptom Assessment during the First 4 Weeks of the Intervention Period
   • Table B9. Follow-up Assessment at 6 Months
   • Table B10. Follow-up Assessment of Interval Medical History at 6 Months

Efficacy
   • Table C1. Biopsy Information
   • Table C3. KC Treatment Information

Safety
   • Table D1. Total Non-Serious Adverse Events (NAEs) and Serious Adverse Events (SAEs)
   • Table D2. Total Non-Serious Adverse Events (NAEs) and Serious Adverse Events (SAEs), by Site
   • Table D3. Non-Serious Adverse Events (NAEs) by System Organ Class (SOC) and Preferred Term (PT)-Excluding Serious Adverse Events (SAEs)
Table D4. Serious Adverse Events (SAEs) by System Organ Class (SOC) and Preferred Term (PT)
Table D5. Non-Serious Adverse Events (NAEs) and Serious Adverse Events (SAEs) by Attributable Event Class
7.0 Subject Disposition Shells
6. Summary of changes to the statistical analysis plan

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<td>V2.0</td>
<td>Deletion of shell tables from pages 32 to 52</td>
<td>Shell tables for the DMC report are now a stand alone document as revisions to these shell tables are ongoing.</td>
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Soe Soe,

In order to guide the statistical analyses so they properly inform the clinical and public health purposes of our CSP562 trial, I put the following items to you:

**CSP562 Highest-priority analyses**

The primary endpoint is KC requiring surgical treatment, and the primary analysis is time to event, which is defined by the date of the biopsy that established the diagnosis that was ultimately confirmed as KC by our reference dermatopathologist.

A key analysis discussed from the outset is to determine any short term efficacy of the intervention, since the intervention would be valuable from the clinical and public health point of view even if its effect dissipated well before the end of the trial. Given the discussion in our earlier phone call about this issue, from which I concluded that there was no good statistical test of outcome that would be other than “exploratory”, and our need to adequately address this outcome, our second analysis should be risk of developing our primary endpoint within one year. Median follow-up in CSP562 was about 2½ years and study examinations were conducted every 6 months.

The third set of high priority analyses is to repeat the above specifically for SCCs, and finally specifically for BCCs. This was also discussed from the outset, and in our written materials is listed as our first “secondary” outcome.

I hope that some of these calculations may be available for our next call.

We should also discuss the other high priority analyses, who will perform them, and when.

Thank you for your work on this

Marty
**Title: Statistical Analysis Plan (SAP)**

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**AUTHOR:** Robert A. Lew, PhD  
**SUBMITTED BY:** Robert A. Lew, PhD

**DOCUMENT/RECORD HISTORY:**

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**AUTHORIZATION SIGNATURES**

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<td>Study Biostatistician</td>
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<td>Clara Kebabian, MPH</td>
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1. INTRODUCTION .............................................................................................................. 2
2. STUDY OBJECTIVES ........................................................................................................ 3
3. INVESTIGATIONAL PLAN .............................................................................................. 4
   3.1. OVERALL STUDY DESIGN AND PLAN .................................................................. 8
   3.2. EFFICACY AND SAFETY VARIABLES .................................................................. 9
       3.2.1 Efficacy endpoints ......................................................................................... 9
       3.2.2 Safety Variables .......................................................................................... 12
4. STATISTICAL METHODS ............................................................................................... 12
   4.1. STUDY SUBJECTS ............................................................................................... 12
       4.1.1 Disposition of Subjects ................................................................................ 12
       4.1.2 Analysis Populations .................................................................................... 13
   4.2. DEMOGRAPHICS AND BASELINE CHARACTERISTICS .................................... 13
       4.2.1 Demographics ............................................................................................... 13
       4.2.2 Medical History and Comorbidities ............................................................. 13
   4.3. GENERAL CONSIDERATIONS ........................................................................... 13
   4.4. EFFICACY EVALUATION .................................................................................... 14
       4.4.1 Primary Efficacy Analysis ............................................................................ 14
       4.4.2 Secondary Efficacy Analysis ....................................................................... 18
   4.4.3 Cost Analysis .................................................................................................... 18
   4.5. SAFETY EVALUATION ........................................................................................ 25
       4.5.1 Mortality ....................................................................................................... 25
       4.5.2 Adverse Events ............................................................................................. 25
   4.6. DETERMINATION OF SAMPLE SIZE .................................................................. 26
   4.7. MISSING VALUES ................................................................................................. 26
   4.8. MULTICLICITY ..................................................................................................... 27
   4.9. INTERIM ANALYSES .......................................................................................... 27
   4.10. DATA MONITORING COMMITTEE ..................................................................... 28
5. REPORTING OUTPUT ..................................................................................................... 28
6. LISTS OF TABLES, FIGURES AND LISTINGS ............................................................. 29
7. SUBJECT DISPOSITION SHELLS ................................................................................. 31
8. BASELINE CHARACTERISTICS SHELLS ................................................................. 29
9. EFFICACY SHELLS ................................................................................................. 29
10. SAFETY SHELLS ....................................................................................................... 29

1. Introduction
Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin, both keratinocyte carcinomas (KCs), account for a half of all cancers in the United States, and over 100,000 cases per year in the VA. Their standard treatment, excision of the lesion, costs the US health care system some $2.5 billion annually and about $100 million annually in the VA. There is no proven means to prevent KCs. An effective prevention strategy would dramatically change the way high risk patients are managed and could substantially reduce the costs of care. We hypothesize that topical 5-fluourouracil (5-FU) chemoprevention will prevent skin cancer and will be cost-saving. To test this we propose a randomized controlled trial of 5-FU compared to a vehicle control to the face and ears. In the study, 1500 veterans at high risk of skin cancer defined as at least 2 KCs in the prior 5 years, at least one of which was on the face or ears, will be randomized to 5-FU or a vehicle control cream, and followed 2 to 4 years. The endpoint will be the incidence of BCCs and SCCs on the face and ears. We will also assess the cost of care, quality of life, and side effects associated with treatment, and the prevalence and number of actinic keratoses, a skin cancer precursor and itself a cause of morbidity and cost. By targeting patients at high risk, the study focuses on high-cost patients for whom this treatment could both improve outcomes (cancers and quality of life) and reduce costs.

2. Study Objectives

Primary Objectives:

To determine the effect of topical 5-FU treatment (compared to a vehicle control treatment) on reducing surgeries for KC on the face and ears. This is to be determined in high-risk patients in a 4 year trial (2 years recruitment; average follow-up 3 years). Everyone in the trial will receive enhanced patient education and free sunscreen for the duration of the trial.

Secondary Objectives:

To evaluate the cost-effectiveness of this intervention, and effect of the 5-FU treatment on the incidence of surgery for BCC, on the incidence of surgery for SCC, on cryotherapy to the face and ears and prevalence of AKs, on quality of life, and on the frequency and severity of specific side-effects of the treatment.

STUDY OUTCOME MEASURES

A. Primary Outcome:
The primary outcome will be the time to diagnosis of the first KC on the face or ears for which surgery is performed. By requiring surgical treatment, we are focusing on the more consequential lesions associated with morbidity and cost for our primary outcome. It should be noted, however, that we expect approximately 91% of the KCs diagnosed in this study to be treated surgically (based on our VATTTC Trial experience), as this is the standard treatment. This outcome uses a time-to-event survival analysis comparing the hazard rates with the two treatments.

B. Secondary Outcomes

Secondary outcomes includes cost-effectiveness, measures of AK's, quality of life, side effects of treatment, lesion locations, and use of NSAIDS. Also, included are outcomes related to the primary outcome such as,

1. Time to occurrence of first BCC for which surgery is performed, and separately of first SCC for which surgery is performed
2. Number of BCCs, SCCs, and overall KCs requiring surgery per person-year of follow-up
3. Time to occurrence of first KC, BCC, and SCC for which surgery is not performed
4. Surgeries not for KC's

3. Investigational Plan

1. **Both groups:**

   All participants will receive patient education about skin cancer, including images of typical early skin cancer lesions, and will be counseled on sun protection and the use of sunscreen. Sunscreen will be provided to the participants free of cost for the duration of the trial. All participants will also be given detailed instructions on how to apply the medication, and shown photographs of a patient with a moderate to severe reaction to 5-FU to illustrate a possible reaction to the study medication.

2. **Intervention group:**

   The intervention group will have topical 5-FU 5% cream applied twice daily for 4 weeks to the face and ears, to be initiated immediately after randomization. The FDA-approved treatment for AKs is twice daily for 2-4 weeks (28 to 56 total doses), and for superficial BCC is 3-6 weeks twice daily (42 to 84 total doses). These two schedules overlap; for this study the treatment duration will be 4 weeks (56 doses). The 5-FU will
only be given once although multiple treatments might potentially be more effective. We expect to be able to detect effectiveness of a single treatment. There are currently no data on which to determine the optimal interval between 5-FU chemopreventive treatments.

We hypothesize that the 5-FU treatment will destroy KC precursors, and because of their slow progression will therefore have a prolonged effect on KC incidence, despite the short course of treatment. The ultimate use of this chemopreventive strategy will undoubtedly involve re-treatment. The data from this study will guide estimation of duration of effect of a single treatment and the appropriate length of a re-treatment interval (see XI.G.1.).

If the participant is unable to tolerate the twice daily 5-FU, they will discontinue the treatment and initiate “cool-down” treatment with triamcinolone 0.1% cream twice daily until the symptoms resolve. In these reactions, symptoms generally resolve within the first 3 days. Asymptomatic erythema typically resolves in about 2 weeks. At 3 weeks after stopping 5-FU, if and only if the participant has not received at least the minimum 2 week (28 dose) course, 5-FU treatment will be resumed on a once-daily basis to complete the 56 dose course. If this is not tolerated, the “cool-down” routine will be followed, but 5-FU will be stopped. It is commonly assumed that the inflammatory response indicates an adequate dose of the topical 5-FU has been received, in which case even those who stop early are likely to benefit from the chemopreventive effect of the experimental cream.

Clinical experience indicates the importance of counseling regarding possible reactions for the successful use of this agent. This counseling will be provided by the on site study nurse, who will talk with all participants at each visit and weekly by phone during the treatment. Study nurses will be trained for counseling prior to use and during use, and for appropriate handling of potential issues that may arise during and after treatment.

B. Assessment schedule

Baseline visit:
- Assess inclusion/exclusion criteria (10 mins)
- Review Informed Consent (15 mins)
- Randomization (5 mins)
- Perform complete skin examination (10 mins)
- Baseline Interview to obtain relevant history (30 mins)
- Quality of Life assessment (10 mins)
Title: Statistical Analysis Plan (SAP)

- Intervention overview (10 mins)
  Telephone interview by study nurse (5 min)
  Weekly during intervention phase
  Once every three months during follow up

Brief follow-up visit at 2 and 4 weeks, and every two weeks thereafter if still on treatment
- Brief face/ears only assessment by study nurse (5 mins)
- Study nurse counseling and focused interview (15 mins)
- QOL assessment (10 mins) at 4 weeks

Follow up visits (every 6 months)
- Complete skin examination (10 min)
- Follow up interview (time since last visit) (15 min)
- If a potential skin cancer is to be biopsied, digital photograph to document precise location; if a surgery has been performed on a KC that had not been photographed, the location will be photodocumented
- QOL assessment at 12, 24, and 36 month visit (10 min)

In order to better illustrate the typical assessment schedule for participants in VA CSP 562, the following figures have been included for review.
Figure 1: Typical assessment schedule for a participant in VA CSP 562. Note: Assumes average follow-up time of 3 years as stated in protocol, and no cool down period.

Figure 2: Assessment schedule for a participant in VA CSP 562 who undergoes a cool down period after initiating treatment for 1 week. As per protocol, the treatment is restarted after a 3 week cool down on a reduced dose of once per day.
Figure 3: Assessment schedule for a participant in VA CSP 562 who undergoes a cool down period after initiating treatment for 2 weeks. As per protocol, the patient has received the minimal dose and treatment is not restarted.

3.1. Overall Study Design and Plan

This trial will be a double-blind, randomized, 4-year, two-arm trial. The trial will test the null hypothesis that the two strategies do not differ with respect to the time-to-event outcome, the first diagnosis leading to surgical treatment of a pathologically confirmed KC lesion.

In terms of the alternative hypothesis we wish to show that:

The 5-FU-based field treatment strategy is effective in the prevention of surgery for a pathologically confirmed KC lesion.

The four-year study can be divided into two periods; namely, a 2-year start-up and enrollment period, a 2-year follow-up period in which patients are only followed. Hence, the length of follow-up time may vary from 2-4 years. Assuming a uniform rate of enrollment the average potential follow-up time will be 3 years.
3.2 Efficacy and Safety Variables

3.21. Efficacy endpoints
PRIMARY HYPOTHESIS

The primary outcome will be the time to diagnosis of the first KC on the face or ears for which surgery is performed. By requiring surgical treatment, we are focusing on the more consequential lesions associated with morbidity and cost for our primary outcome. It should be noted, however, that we expect approximately 91% of the KCs diagnosed in this study to be treated surgically (based on our VATTTC Trial experience), as this is the standard treatment. This outcome uses a time-to-event survival analysis comparing the hazard rates with the two treatments.

Since we are evaluating chemoprevention, the primary outcome is surgery for primary lesions, not recurrent lesions. Recurrent lesions are recognized by their occurrence in the scar from prior removal of the cancer. We understand that recurrent lesions occur when malignant cells remain after removal or destruction of a KC, and those cells are frequently deep in the skin and therefore less suitable for treatment with topically applied agents.

This endpoint will be ascertained either at the scheduled follow-up examinations or at examinations requested by the patient. At each study visit, the participant will be questioned about any skin cancers or surgeries. Any potential KCs designated for surgical intervention will be noted for later tracking on Form 10: KC Treatment, and the VA electronic record will be checked to ascertain or confirm the occurrence of the KC and the surgical procedure. For all participants in the trial, all pathology reports of biopsies from the skin of the face or ears will be reviewed at the chairman’s office to determine the diagnosis of all lesions biopsied or otherwise surgically removed, and all of the histopathologic specimens surgically removed lesions will be reviewed by the central dermatopathologists. If a surgically excised lesion has the diagnosis of KC on initial biopsy, subsequent re-excision or Mohs surgery layers slides will not be sent for central review, since the lesion already has a centrally reviewed diagnosis of KC and hence qualifies as an endpoint. Skin cancers diagnosed outside of the VA, and associated surgeries, will be systematically sought in all participants to insure that our outcome measure is complete. For any outside diagnosis or surgery, the medical record will be sought and reviewed. In the VATTTC trial, 91% of KCs biopsied had a subsequent surgical treatment (some variety of excision or electrodesiccation and curettage), and diagnosis of KCs on the face and ears outside of the VA system represented only 1% of the total number of KCs on the face and ears during that 6-year trial.
We will use actual cancer occurrence for which surgery is performed, as opposed to occurrence of a precursor or intermediate marker, as the primary outcome because of the problems in the in reliability of diagnosis and counting precursor lesions\(^{36}\), their variable natural history, which includes a high probability of apparently spontaneous resolution, and a small probability of progression to invasive cancer\(^{2,5}\).

The null hypothesis is that the two treatment groups (5-FU intervention and control therapy) do not differ in their time-to-event hazard rates. The alternative hypothesis is that intervention has a lower hazard rate than control therapy with a hazard ratio for control therapy compared to intervention exceeding 1.42.

**NULL HYPOTHESIS**

The null hypothesis is two-sided and thus we would reject the null hypothesis if the hazard ratio exceeded 1.42 or was less than 1/1.42 = 0.7, but only the former event would be deemed a success.

In summary, the design compares two treatments and the study outcome is the first diagnosis leading to surgical treatment of a pathologically confirmed KC lesion.

**SECONDARY OUTCOMES**

1. **Cost-effectiveness of the treatment strategy:** It is common for susceptible individuals to have multiple AKs and KCs. The cumulative resources devoted to their care and specifically the treatment costs are large (see I.B). The cost analysis will therefore look at potential short-term and long-term savings from this strategy in high-risk populations (see VII). KC treatments other than surgery, which are expected to be few, will also be included in this assessment.

2. **Time to occurrence of first BCC for which surgery is performed, and separately of first SCC for which surgery is performed:** The etiologic differences between BCC and SCC indicate that a chemopreventive intervention may have differential effects between the two histopathologic types of KC. As reviewed in Section I, there is substantial evidence that the proposed intervention will be effective for both histologic types. Since there are identifiable populations at greater risk for BCC, and others for SCC, delineating the value for each separately is worthwhile. We will also examine predictors of BCC and SCC occurrence.

3. **Number of BCCs, SCCs, and overall KCs requiring surgery per person-year of follow-up:** Because patients often will have multiple KCs, we will evaluate the number of BCCs, SCCs, and KCs per person-year of follow-up. This may show that the treatment reduces the overall numbers of KC over time.
4. **Time to occurrence of first KC, BCC, and SCC for which surgery is not performed.** This will allow us to determine any effect of the study intervention on a later decision to treat a skin cancer surgically, instead of by an alternative modality. The numbers not treated surgically are expected to be small (about 9% of KCs diagnosed), so only an (unexpected) large effect could be noted in this analysis.

5. **Measures of AKs:** We will also measure AKs because the morbidity and cost associated with these skin lesions is large (see section I). Also, the intervention tested has known efficacy against AKs, so reduced AKs and reduced need for treatment of AKs may be important benefits of the regimen. We will count AKs greater than 5 mm in diameter, a reliable measure. We will also count and measure cryotherapeutic treatments as an outcome; this is the standard treatment for AKs. Cryotherapy treatments will be a component of the cost-effectiveness analysis. Any treatments for AKs other than cryotherapy will also be measured.

6. **Surgeries not for KC:** We will examine whether there is a difference between groups in surgery on the face and ears for lesions other than KC. This will also be a component of the overall cost-effectiveness analysis.

7. **Side-effects of treatment:** Specific indices of chemopreventive treatment side-effects (especially pain, itch, sores/crusts, and erythema) will be ascertained. The measurement will include questions regarding the presence and degree of symptoms such as pain/burning and pruritus of the face and ears as well as erythema.

8. **Quality of life:** Skin cancer can cause substantial anxiety, disfigurement, and other morbidity. For quality of life, we will use the Skindex (a published, validated, widely used quality of life instrument for skin disease). This is a brief questionnaire completed by the participant.

Morbidity from KC may include both morbidity from the cancer and from the treatments. When cancer is diagnosed, treatment of AKs may result in short-term pain and long-term depigmentation that may be disfiguring. Hence the quality of life measure reflects morbidity due to the skin cancers, morbidity due to AKs, morbidity due to their treatment, and morbidity due to the chemoprevention interventions themselves.

9. **Exploratory analysis of endpoint location:** We will review photographs of endpoint lesions to ascertain any particular sub-areas on the face and ears at which the chemopreventive treatment may have been more or less effective.
10. **Nonsteroidal anti-inflammatory medications (NSAIDs):** We will assess use of NSAIDs (OTC and prescribed) to evaluate their relation to KC risk, since that association has been suggested but is controversial.\textsuperscript{45,46}

**Study procedures related to unblinding the study**

During the study, the accumulative study data will encode the two treatment strategies as ‘A’ and ‘B’. All analyses by treatment will be blind; that is, the treatments will only be identified as ‘A’ and ‘B’. When the study ends and subsequently the final dataset is locked, then the treatments will be unblinded so that the analysts and the principal investigator can write the primary paper. In the unusual circumstance that the DMC requests the data be unblinded before the study ends, the only MAVERIC staff members to be unblinded will be the 1) statistician responsible for the primary analysis, and 2) as few other persons needed to interpret the results of analyses requested by the DMC. Staff who directly deal with the day-to-day data will not be unblinded. The director of MAVERIC will determine whom to unblind as appropriate to the specific DMC request. A record to file will list those persons and the date they were unblinded.

3.2.2 **Safety Variables**

The safety variables are the serious adverse events; namely death, hospitalization, other SAE’s. In addition, safety outcomes include all adverse events related and unrelated to treatment.

4. **Statistical Methods**

4.1 **Study Subjects**

4.1.1 **Disposition of Subjects**

The number of subjects screened, enrolled, and completing the study will be presented overall and by center subdivided by demographic categories (i.e., gender, race, etc.)

Reasons for the early termination of subjects as noted on the CRF will be summarized. Subjects that are lost to follow-up will be summarized as one category.

The following listings will be provided:
A by-subject listing of completion/termination details
A by-subject listing of protocol violations and deviations

4.1.2 Analysis Populations
All enrolled subjects will be included in the subject listings (by study ID number).

All eligible subjects who gave consent will not be included in the analysis. Only subjects who begin to receive treatment will be included in the safety (safety population) and efficacy (efficacy population) analyses.

4.2 Demographics and Baseline Characteristics

4.2.1 Demographics
Demographic details (e.g., age, sex, ethnicity, race, marital status, and smoking status) will be summarized overall and by center.

4.2.2 Medical History and Comorbidities
The pertinent medical histories (i.e., comorbidities), and history of AKs and skin cancer will be summarized overall and by center. (frequencies and percentages will be given).

4.3 General Considerations
In general the number of observations, mean, median, standard deviation, minimum, and maximum will be calculated for continuous variables. The number of decimals place will be as follows: minimum and maximum to the same number of decimal places as present in the raw data, mean and median to plus one decimal place, standard deviation to plus two decimal places. Frequencies and percentages will be calculated for categorical data.

Baseline is defined as the baseline assessment visit.

Missing endpoint data will not be imputed. Missing covariate data will be imputed in selected circumstances as described below.

All planned analyses for the final clinical study report will be performed using a two-sided nominal significance level of 0.05; however, comparisons less than 0.10 will also be discussed as being marginally significant.
4.4 Efficacy Evaluation

4.4.1 Primary Efficacy Analysis

The study will enroll a total of 1000 patients, 500 of whom will receive the topical 5-FU-based treatment, and 500 of whom will receive the control treatment. We will enroll 500 patients per year for two years to accrue 100 patients per site at 10 VA medical centers.

The outcome measure distinguishes between surgical excisions of a pathologically confirmed KC lesion (either BCC or SCC lesion) and the rare excisions that result in any other diagnosis. Because chemoprevention may have no effect on other lesions, only KC lesions will be counted for the primary outcome.

The primary outcome measure is:

The time after enrollment in the study until the first diagnosis leading to surgical treatment of a pathologically confirmed KC lesion.

In terms of the alternative hypothesis we wish to show that:

The 5-FU-based field treatment strategy is effective in the prevention of surgery for a pathologically confirmed KC lesion.

A. The Primary Outcome:

The null hypothesis is that the two treatment groups (5-FU intervention and control therapy) do not differ in their time-to-event hazard rates. The alternative hypothesis is that intervention has a lower hazard rate than control therapy with a hazard ratio for control therapy compared to intervention exceeding 1.42.

This four-year study will enroll patients for 2 years so that the last patient enrolled will potentially have up to 2 years of follow-up. The first patient enrolled will potentially have up to 4 years of follow-up. On average, patients will potentially have approximately 3 years of follow-up. Thus, the power calculations are based on estimates of a surgically treated diagnosis of KC within 3 years.

Based on the VATTC study we expect the 3-year rate of surgical excision of a pathologically confirmed KC lesion will be 44%. This is a VATTC incidence rate as opposed to a surgery rate, but these will negligibly differ.

We have chosen a 3-year of 42% for the outcome, surgical excision of a pathologically confirmed KC lesion. We make this 2% reduction for several reasons. First, a rare patient who developed both a SCC and a BCC at the same
time will only be counted once. Second, in the proposed study, the 3-year incidence rate for KC may be slightly reduced because of differences between the old VATTCC protocol and the proposed protocol. In the proposed trial physicians will adhere to their internal policies and tend to systematically remove many of AK’s with cryotherapy and thereby may lower the 3-year KC rates. In the VATTCC trial, centers were asked to take a watchful waiting policy on most AK’s, but tended to follow their own internal policies on this matter. Third, for the proposed trial we will exclude patients who had 5-FU treatment during the 3 years prior to enrollment, and we speculate that these patients may be at higher risk for KC’s than the eligible patients. To account for these three factors we assume that the KC rate for the proposed trial will be 95% of the VATCC rates.

Under the null hypothesis:

The three-year KC surgery rate will be 42%

Under the alternative hypothesis for patients treated with 5-FU:

The three-year KC surgery rate will be 32%

The reductions attributed to treatment may be viewed in several ways. The absolute reduction from 42% to 32% is 10%, the relative reduction is \((42 - 32)/42 = 24\%\), and the hazard ratio (control hazard rate/treatment hazard rate) of 1.42 midway between the simple odds ratio, \(42(100-32)/(32(100 - 42)) = 1.54\) and the risk ratio \(42/32 = 1.31\).

Sample Size and Statistical Power Considerations

The results for the KC primary outcome measure, time until first SCC diagnosis, will be analyzed by means of the two-sided log-rank test to detect either a hazards ratio that exceeds 1.42 or is less than \(1/1.42 = 0.74\). The test will have a two-sided 4.8% type I error. (When added to the interim analysis that has a 0.2% Type I error, the overall type I error is 5%). The test has 90% power to detect a ratio of hazards of 1.36 or larger or 0.70 or less with a total of 1000 patients, 500 per study arm. This assumes that 8% of the patients either die or are lost to follow-up while on-study before a SCC diagnosis can be observed. The power for the log-rank test was computed using Schoenfeld’s formula (see equation 18.10 in Buyse, Staquet and Sylvester, 1984).

Interim Analysis
We will perform one interim analyses when the first 500 patients (250 in each study arm) enrolled have completed two years of follow-up. Assuming a uniform rate of enrollment over time this interim analysis should take place at the end of year 3. With an 8% loss-to-follow-up rate each study arm will have 210 evaluable patients.

The one interim analysis carried out when the 500th patient completes two years of follow-up has a small effect on overall type I error. The interim analysis has a Type I error of 0.2%. The interim analysis is two-sided, but the interim null hypothesis will only be rejected if the hazard ratio exceeds 2.39. If the hazard ratio is less than 1/2.39 = 0.42 then trial will be stopped for futility.

After 3 years the first patient entered will potentially have 3 years of follow-up and the last patient entered will potentially have 1 year of follow. Thus, the average potential follow-up will be two years. If we expect a 44% KC rate at three years then under the exponential model we would expect a 32% KC rate at two years.

Under the interim analysis null hypothesis:

The two-year KC rate will be 32%

Under the interim alternative hypothesis for patients treated with 5-FU:

The three-year KC rate will be 16%

The reductions attributed to treatment may be viewed in several ways. The absolute reduction from 32% to 16% is 16%, the relative reduction is (32 - 16)/32 = 50%, and the hazard ratio (control hazard rate/treatment hazard rate) is 2.39.

We considered earlier times for interim analyses, but rejected this idea because sample sizes on the order of 150 per study arm only have modest power to detect very large effects.

For both the interim analysis and the primary analysis we considered the possibility that the effect of 5-FU merely delays the clinical emergence of a KC by a short period, such as 6 months. Then a wide gap between control and treatment arms, due to lower incidence in the treatment arm, might rapidly narrow with more follow-up. Indeed, this possibility led us to propose to monitor VA electronic records and passively follow patients after the four-year study ends to detect such narrowing. Finally, compared to other types of cancer KC's are seldom fatal, so that the evaluation of costs to the VA and patient morbidity assume greater importance. We expect that to gather the data for these evaluations would prolong the trial past the early stopping date.
Data Analysis Plan

The primary outcome hypothesis will be tested using a two-sided log-rank test to compare the hazard rate for one treatment group to that for another treatment group. A significant difference showing that the intervention strategy compared to the control decreases the hazard of surgery for pathologically confirmed KC will be regarded a positive result, whereas a result that shows intervention does not significantly differ from or, in fact, significantly increases the hazard rate will be regarded as a negative result. We will report the hazard rates, their ratio and the 95% confidence interval about the ratio.

The SAS code for this analysis is:

```
proc phreg data = c562.final_date;
model followup*primary(0) = txb / rl;
title "Basic model - Cox model";
```

In this code the dataset is dated to coincide with the data freeze date for DMC meeting. ‘Followup’ refers to time until surgery. Primary has two values: 0-censored and 1-surgery.

This will be followed by further refined analyses, using multiple linear Cox proportional hazards regression modeling, to take account of the effects of baseline covariates on the primary outcome measure. Covariates will include demographic and clinical factors (age, sex, smoking status, education, number of AK’s, history of BCC, of SCC, or both).

The regression modeling we shall employ will include a model with treatment by covariate terms to explore the possibilities of treatment by covariate effects (that is, exploration of potential subgroup effects). We will test the proportional hazards assumption by including a time-treatment interaction term in the model. We will use graphic methods to study goodness-of-fit as described in section VII.3.1 of the text ‘Statistical Models based on Counting Processes (Anderson K, Borgan O, Gill RD, and Keiding N, Springer-Verlag New York 1991).

Extended Follow-Up

The four-year study can be divided into two periods; namely, a 2-year start-up and enrollment period, a 2-year follow-up period in which patients are only followed. Hence, the length of follow-up time may vary from 2-4 years. Assuming a uniform rate of enrollment the average potential follow-up time will be 3 years.

The power calculations account for both the varying amount of follow-up time and for the censoring of outcomes. Varying follow-up time and the length of the recruitment
period have negligible effects on power. We have assumed an 8% rate of lost-to-follow-up combining the on-study death rate with the study lost-to-follow-up rate. Hence, the statistical power calculation is based on the 920 evaluable patients among the total of 1000 enrolled.

When the study ends after 4 years we will continue for one year to follow patients who have not had a new KC surgery by tracking the medical procedures they have as reported in the VA Austin database. We will look for an excess of KC surgical events in the 5-FU treatment arm indicative of events delayed by treatment as opposed to prevented by treatment.

4.4.2 Secondary Efficacy Analysis

Secondary analyses are of several types; analyses directly related to the primary hypothesis of BCC and SCC surgical endpoints, quality of life as measured by the Skindex instrument, multiplicity of AK’s, and cost analyses. Cost analyses are described in section VII.

Time to surgery for a new BCC and for a new SCC:

In analyses directly related to the primary hypothesis, we will disaggregate KC into its components BCC and SCC. Then we will compare the treatments with respect to each of the two separate outcomes of the time to a diagnosis leading to surgery for a new SCC and time to a diagnosis leading to surgery for a new BCC using the analogous time-to-response analysis delineated for the primary analysis. For this secondary outcome each of the two parallel null hypotheses is that the two treatment groups (intervention and control therapy) do not differ in their time-to-event hazard rates. As in the primary analysis, we will begin with the two-sided log-rank test for each of the two outcome measures, time until the first BCC diagnosis leading to surgical treatment of a pathologically confirmed SCC lesion and time until the first BCC diagnosis leading to surgical treatment of a pathologically confirmed BCC lesion.

We will carry out two additional time-to-event analyses of the aggregated KC outcome. We will apply the log-rank test to the data obtained from the extended follow-up beyond 4 years as in the primary analysis. This analysis will be done on both the final data set when the trial ends and on the extended follow-up data set. For each of these analyses we will report the hazard rates, their ratio and the 95% confidence interval about the ratio. This will be followed by further refined analyses, using multiple linear Cox proportional hazards regression modeling, to take account of the effects of baseline covariates on the primary outcome measure. Covariates will include demographic and
clinical factors (age, sex, smoking status, education, number of AK’s, and history of BCC, of SCC, or both. The regression modeling we shall employ will include a model with treatment by covariate terms to explore the possibilities of treatment by covariate effects (that is, exploration of potential subgroup effects).

These secondary analyses are exploratory in nature and thus we have not assigned it a level of power. Extensive exploratory analyses will address the issue of the optimal time interval between applications of 5-FU therapy. Assuming that one 5-FU treatment reduces the hazard of surgical outcomes, we will separately study the disease endpoints of BCC, SCC, and KC to determine the shape of the hazard rate over time for the 5-FU treated and control patients. The objective will be to estimate the hazard rate for a new BCC, SCC, or KC in the treated and untreated groups. We will use an extension of the proportional hazards model, specifically with a Weibull frailty model that provides an explicit model for the hazard rate. In particular, we will test whether the hazard rate for patients treated with 5-FU remains flat or rises over time. This would address the question of whether 5-FU treatment delays the incidence of new KC’s. Relative to the hazard rate among controls and to a flat hazard rate, the pattern of a rising hazard rate over time would indicate that 5-FU delayed KC incidence. If 5-FU is effective then the pattern of a flat hazard rate over time would indicate destruction of a proportion of KC’s but not delay.

**Quality of Life:**

We will compare the treatments with respect to the change in the Skindex score after one year and after two years. The change after one-year is the difference between the one-year score and the baseline score. The change after two years is the difference between the two-year score and the baseline score. Regarding these changes as continuous outcomes, we will use Student’s t-test to compare the treatments. Controlling for the covariates listed above we will carry out a linear regression analysis with treatment as the major factor. Confirmatory analysis will be done using combining the one-year, two-year, and three-year change scores into a repeated measures regression analysis. This analysis will treat the factor subject as a random effect and explore the possibility of different sizes of effect within each follow-up year.

**Burden of Actinic Keratoses:**

We will evaluate the effect of study treatment on the burden of actinic keratoses on the face and ears, as assessed by counts of large lesions, >= 5 mm in diameter. For the analyses of counts and for the number of spot treatments we will fix the follow period at two years and carry out a simple Poisson regression comparing the treatments and a more complex Poisson regression comparing the treatments and controlling for covariates. For the analyses of estimates of skin area affected (a continuous outcome) we will fix the follow period at two years and carry out a Student’s t-test comparing the
treatments and a more complex linear regression comparing the treatments and controlling for covariates. To confirm this analysis we will collapse the Poisson counts into ordinal categories; none, 1-3, 4-10, 10 or more. We will rerun the analysis using polytomous logistic regression. For each of the proposed analyses viewing baseline and each follow-up year as repeated measures we will also analyze the data with subject as a random effect using the SAS procedure NLMIXED.

4.4.3 Cost analyses

Cost-effectiveness of the treatment strategy: It is common for susceptible individuals to have multiple AKs and KCs. The cumulative resources devoted to their care and specifically the treatment costs are large. The cost analysis will therefore look at potential short-term and long-term savings from this strategy in high-risk populations (see VII). KC treatments other than surgery, which are expected to be few, will also be included in this assessment.

Design Considerations for the Economic Analysis:

There are two components of the proposed economic analysis. First, we will conduct a cost-effectiveness analysis from both a VA and a societal perspective. Second, we will conduct a business impact, or cash-flow analysis from a VA perspective. The purpose of this second analysis will be to provide VA managers with the information that they need to accurately determine the financial impacts of adopting the study protocol as standard therapy. Both of these analyses are conditional on the main outcome of the study being an effective intervention. If the intervention doesn’t work, the economic analyses are moot, as the intervention will not be clinically adopted.

Skin cancer is a condition for which the treatment can be clearly separated from the treatment of other conditions. Thus, this study will not consider other health care costs; we will assume that the randomization equalizes these across the two study arms. The one exception to this is if a skin cancer metastasizes to another site. The costs and utilization associated with the treatment of metastatic cancers will be considered, conditional on site investigator verification that the metastatic cancer is related to BCC or SCC.

Preliminary calculations based on the effect sizes that the study is powered on project a cost savings associated with the intervention. Further, these cost savings will persist for a wide range of assumptions about the costs of therapy and the effectiveness of the intervention. Thus, there will only be conditional collection of health utilities information. If the initial analysis at the end of the trial show that we need to value the relevant health state utilities, we will submit a supplemental proposal to CSSMRB for the collection of
health utilities. Study information from the skin cancer-specific quality of life measures collected during the study, will be used to determine the health states that need to be valued. Community ratings will be obtained for these health states. Since study subjects are not required for this method of utility assignment, the collection of the utility data can be deferred without jeopardy to the proposed analysis.

**Sources of Cost and Utilization Data**

VA costs will be captured from the VA Decision Support System (DSS) National Data Extracts (NDEs). DSS is a comprehensive, activity-based hospital accounting system that VA uses to track its costs. Summary extracts are made from this system that tract inpatient, outpatient, and pharmacy costs. These data are extracted and converted to SAS datasets at the VA Austin Automation Center (ACC) on an annual basis. They are usually available in February of each year.

Encounter data with ICD-9-CM codes for all encounters, and CPT codes for outpatient encounters are also available from the National Patient Data Base SE file at the ACC. These data will allow centralized tracking of all VA patient care encounters.

At many VA facilities at least some of the skin cancer-related care (especially Mohs surgery) is provided as contract care. To ensure complete data for this care, each site will be asked to identify the types of care that they routinely provide under contract or fee-basis care. Study forms will be used to capture the CPT codes for all fee-basis and contract care. While there are centralized databases of fee basis care, these data have never been carefully assessed for completeness. Further, starting in FY 2007, all fee-basis and contract care is supposed to be captured by DSS. Once the FY 2007 DSS extracts are available in early 2008, HERC will compare the data reported on the study forms with the fee-basis and contract care reported in DSS. If the DSS is found to accurately capture these data, use of the study forms for contract and fee-basis care will be discontinued.

**Non-VA Health Care**

Prior experience from CSP #402 found that 99% of the KC-related care was VA provided. Thus, while patients will be asked to self-report their use of related care obtained from a non-VA provider, the impact of errors of patient self-reporting will be minor. At enrollment, patients will be asked to bring copies of the billing statements for any non-VA skin cancer-related care to each subsequent follow-up visit. At each follow-up visit, the site coordinator will ask the patient if any non-VA skin cancer-related care was received since the last visit. If the patients does not provide copies of the billing statements, the site coordinator will use a study form to determine what non-VA care was provided. Fortunately, there are only a few types of patient care encounters that
are relevant care. Thus, the study form will list each of the types of service. VA averages for these types of encounters will be used to assign costs to these encounter types. Patients will also be asked for the date of service. These self-reported uses of non-VA care will be cross-checked with the VA databases, especially the fee-basis files, to prevent double counting.

Patients will also be asked at enrollment if they are currently enrolled in Medicare (median age for CSP #402 was 71). If they are not currently enrolled in Medicare, they will be asked if they expect to enroll in Medicare during the study period. The consent form will include permission to access Medicare records. A finder file of all study patients will be submitted to VIREC, which is the VA repository of the Medicare data for users of VA care. These Medicare data will be used as a further check for study relevant non-VA health care utilization. Given the lag in the linking of the Medicare data to VA users, the Medicare data may not be available for the last year of the study at the time of analysis. But, the Medicare data will provide data for earlier years of follow-up and allow the assessment of the completeness of the patient self-report of use of non-VA care.

Assumptions for Preliminary Cost Analysis:

The VA cost of 5-FU was obtained from the April 2007 list of current VA drug prices maintained by the VA Pharmacy Benefits Management (PBM) group. It was assumed that two 40g tubes of 5-FU would be sufficient for each course of chemo-preventive therapy. The April 2007 cost of a 40g tube of 5-FU was $80.42, yielding a per treatment cost of $160.84. The CPT codes were identified for Mohs facial surgery, and the 2005 VA frequency of use of these codes identify their relative use in VA. Using 2006 Medicare RVUs, conversion factors, and APC facility payment rates, we calculated an average cost of $830. This cost decreases to $715 if the surgery is done in conjunction with one of the more expensive types of reconstructive surgeries due to the facility payment methodologies for ambulatory surgery.

To estimate the VA costs for reconstructive procedures, we examine the “repair” codes recorded in VA encounters where Mohs surgery was performed. We used the weighted average of these payments, with adjustments for the Medicare facility payment methodology to obtain a weighted average VA cost for Mohs surgery and reconstruction of $1573.

Based on the information from CSP 402 and a search of centralized VA data, we know that the patients who will be enrolled in this trial have a high incidence of AK, which will almost always be treated with cryosurgery. Again, we used the actual VA use of CPT codes to calculate a weighted average cost for a cryosurgery of $138.
While it is possible that the intervention will reduce other VA costs of care, no other potential savings were included for this preliminary analysis. We acknowledge that there will probably be some added costs of the intervention for following up with patients by telephone during the intervention period. These will be captured during the actual analysis, with care to make sure that they exclude the additional visits/contacts that were part of the research project, not actual patient care. The cost of the initial visit at which the 5-FU is dispensed will not be included as this would be done at a regularly scheduled annual encounter for these high-risk patients.

From the power calculation of this trial, we are conservatively projecting an absolute reduction of 11% in the number of KC that will require surgical treatment. For the base analysis, we also assumed that on average, 0.75 cryotherapy treatments per patient would be averted. This is a fairly conservative assumption, given that 5-FU is known to be an effective therapy for AK and the study patients average more than 1 AK per year, with an average follow-up of 3 years. These assumptions result in a net savings of $116.

We also tested the sensitivity of these assumptions. If no reductions in AK therapy are assumed, the net savings, due solely to the reduction in Mohs surgery is $13. With the 0.75 cryotherapy treatments averted per patient for the treatment of AK, there are net savings as long as the reduction in the need for surgical treatment for facial KC is greater than 3.6%. Net savings also remain with 0.5 cryosurgeries averted per patient as long as the reduction in surgical treatment for facial KC is at least 5.8%.

The cost-effectiveness analysis will be an intent-to-treat analysis, using an incremental cost-effectiveness ratio, and a societal perspective. All costs and benefits will be discounted at a 3% rate. We will monitor the development of the emerging concept of presenting the results in terms of a net health benefit, and will consider this method as an alternative for presenting the results. Essentially, we are acknowledging that this new method could change the consensus on how to report cost-effectiveness studies, and that we will be sensitive to this possibility.

Because this is a VA trial, the cost-effectiveness analysis will be repeated from a VA perspective. This will be done by revising the final analysis to only include the costs directly incurred by VA. This will have no affect on the QALY expressed benefit to the study subjects.

Given the strong prior that the study results will show the intervention to be effective and have a net cost savings (i.e. strong dominance), the utility/QALY assessment will be conditional. The changes in net health utilities associated with the different therapies in this study are likely to be relatively small. Standard indirect utility instruments such as the HUI and the EQ-5D are unlikely to be sensitive enough to detect these changes.
The study will regularly collect data using disease-specific quality of life instruments. These instruments will provide sufficient information to allow the characterization of the health states that are most relevant to the study. If the initial analysis at study close-out shows that the net costs of the intervention may be positive, then supplemental funding will be requested to allow the outcomes from the disease-specific quality of life instruments to be mapped to utilities. These utilities will be assigned using a community sample of healthy adults. The study economist has prior experience with this method; he worked with colleagues at Stanford University to obtain community-rated utilities for the Activities of Daily Living scores that were used to measure patient functioning for Geriatric Evaluation and Management patients in CSP #006. Application of this method will allow utilities to be assigned to the disease-specific quality of life measures that will be recorded for study subjects at regular intervals. The advantage of this approach is that it avoids the significant expense of assigning utilities to health states unless it is necessary for the completion of the analysis.

We also acknowledge the possibility that the interventions have differential effects on patient quality of life that could be the opposite of our expectations. The intervention will treat all patients to prevent the occurrence of KC in some patients (the intervention will also prevent the occurrence of AK in a larger fraction of patients). Thus, all of the intervention patients will experience some disutility associated with the treatment, while only a subset will receive the utility benefits of averted KC or AK. While the hypothesis is that the intervention arm will result in net higher disease-specific quality of life ratings, we will examine the results to confirm this. If the results of the disease-specific quality of life ratings don’t clearly show a net benefit to the intervention arm, this would also trigger the collection of utilities data from a community sample.

**Cash-Flow Analysis:**

The VA is operated on a fixed global budget. VA managers must make decisions on where and how to allocate fixed resources. While traditional clinical trials results can make a compelling case about the effectiveness of an intervention, they don’t provide all of the information that managers need to implement the adoption of new technologies or treatments. Even if this study has the expected outcome of a net savings attributable to the intervention, this alone will not provide sufficient information for VA managers. This is because the study intervention requires an up front investment in chemo-preventive therapy. The up front costs will not be fully recouped in the first year. To allow VA managers to adequately plan for the adoption of chemo-preventive 5-FU therapy, we also plan to use the study data to calculate the expected cash flow affects of implementing the study intervention. We will use the actual utilization of care for patients in the control arm of the study to project when the averted treatments would have occurred, in terms of months since initiation of 5-FU treatment. These will be summarized on a quarterly basis, and compared with the cost of 5-FU therapy.
HERC has planned to include this type of cash-flow analysis in other CSP trials that are already in progress. The intent is to work with various VA leadership organizations to help disseminate this information. If this trials shows the intervention is effective, we will build on these previous management dissemination efforts. The purpose of this type of analysis is to make the results as useful as possible for VA managers. Feedback from this type of effort for other CSP trials will be incorporated into the exact dissemination plan.

4.5 Safety Evaluation

All safety summaries will be based on the Safety Population described in Section 4.1.2 “Analysis Populations.”

4.5.1 Mortality

The frequency and proportion of all deaths will be presented overall and by center.

A by-subject listing will be provided.

4.5.2 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 9.0) coding dictionary.

All AE summaries will be based upon the number of subjects reporting AEs and not the number of events reported. Adverse events (AEs) will be tabulated (i.e., those events that were not present at the baseline evaluation or worsened in severity following the start of treatment). Any AEs starting after study completion or withdrawal will not be tabulated.

If the AE start date is not a complete date, the following rules will be applied to determine whether the AE will be tabulated or not.

If the start date is completely missing:
- The AE will be tabulated unless the AE stop date is less than the baseline date.

If the day part of the AE start date is missing, use the following algorithm:
- If the month and year of the start date are later than or equal to the month and year of the surgery, then the AE will be tabulated. If the month and year of the stop date are earlier than the month and year of the surgery, then the event will be assumed to not be tabulated.
If the day and month of the start date are missing, use the following algorithm:
- If the year of the start date is later than or equal to year of the surgery, then the AE will be tabulated. If the year of the stop date is earlier than the year of the surgery, then the event will not be tabulated.

The number and percentage of subjects with AEs through the end of the study (analysis period) will be summarized by system organ class and preferred term overall.

Summaries of AEs by intensity and relation to study device will be presented by system organ class and preferred term overall. For each subject and each AE, the worst intensity/relation recorded will be attributed and used in the intensity/relation summaries. If intensity/relation is missing, the intensity/relation will be queried by data management.

The number and percentage of subjects with serious adverse events (SAE) through the end of the study (or analysis period) will be summarized by system organ class and preferred term overall.

A by-subject listing of all AEs will be provided.

A by-subject listing of all serious AEs will be provided.

4.6 Determination of Sample Size for the Primary Hypothesis

The results for the KC primary outcome measure, time until first SCC diagnosis, will be analyzed by means of the two-sided log-rank test to detect either a hazards ratio that exceeds 1.42 or is less than 1/1.42 = 0.74. The test will have a two-sided 4.8% type I error. (When added to the interim analysis that has a 0.2% Type I error, the overall type I error is 5%). The test has 90% power to detect a ratio of hazards of 1.36 or larger or 0.70 or less with a total of 1000 patients, 500 per study arm. This assumes that 8% of the patients either die or are lost to follow-up while on-study before a SCC diagnosis can be observed. The power for the log-rank test was computed using Schoenfeld's formula (see equation 18.10 in Buyse, Staquet and Sylvester, 1984).

4.7 Missing Values Primary Analysis

Dropouts will be included in the primary analysis assuming random censoring but sensitivity analyses will address their potential that non-random censoring patterns
biased the results. Imputation of final outcomes requires questionable assumptions about treatment effects. We will consider a range of such assumptions in the confirmatory analyses. The confirmatory secondary analysis including the dropout data censored at the appropriate study visit will also be done to assess potential bias associated with the complete case analysis.

A covariate adjusted primary analysis will be done in order to either confirm or not confirm the primary analysis that has no covariates. In either case, the confirmatory analysis will indicate the degree of bias in the complete case analysis.

Practical measures will be taken to minimize missing values and losses to follow-up. One prominent conjecture about patients who drop out is that they tend to have poor outcomes. This clearly would violate the assumption of missing-at-random. Multiplicity

There will be no corrections done for multiple comparisons in this descriptive study.

4.8 Interim Analyses
We will perform one interim analyses when the first 500 patients (250 in each study arm) enrolled have completed two years of follow-up. Assuming a uniform rate of enrollment over time this interim analysis should take place at the end of year 3. With an 8% loss-to-follow-up rate each study arm will have 210 evaluable patients.

The one interim analysis carried out when the 500th patient completes two years of follow-up has a small effect on overall Type I error. The interim analysis has a Type I error of 0.2%. The interim analysis is two-sided, but the interim null hypothesis will only be rejected if the hazard ratio exceeds 2.39. If the hazard ratio is less than 1/2.39 = 0.42 then trial will be stopped for futility.

After 3 years the first patient entered will potentially have 3 years of follow-up and the last patient entered will potentially have 1 year of follow. Thus, the average potential follow-up will be two years. If we expect a 44% KC rate at three years then under the exponential model we would expect a 32% KC rate at two years.

Under the interim analysis null hypothesis:

The two-year KC rate will be 32%

Under the interim alternative hypothesis for patients treated with 5-FU:

The three-year KC rate will be 16%
The reductions attributed to treatment may be viewed in several ways. The absolute reduction from 32% to 16% is 16%, the relative reduction is \((32 - 16)/32 = 50\%\), and the hazard ratio (control hazard rate/treatment hazard rate) is 2.39.

We considered earlier times for interim analyses, but rejected this idea because sample sizes on the order of 150 per study arm only have modest power to detect very large effects.

For both the interim analysis and the primary analysis we considered the possibility that the effect of 5-FU merely delays the clinical emergence of a KC by a short period, such as 6 months. Then a wide gap between control and treatment arms, due to lower incidence in the treatment arm, might rapidly narrow with more follow-up. Indeed, this possibility led us to propose to monitor VA electronic records and passively follow patients after the four-year study ends to detect such narrowing. Finally, compared to other types of cancer KC’s are seldom fatal, so that the evaluation of costs to the VA and patient morbidity assume greater importance. We expect that to gather the data for these evaluations would prolong the trial past the early stopping date.

4.9 Data Monitoring Committee

Data and study progress will be monitored by the study executive committee and by the study steering committee. The Data Monitoring Committee will review the study progress and safety on at least an annual basis with additional meetings and communications as needed.

5.0 Reporting Output

All outputs will be produced using SAS Version 9.1 or a later version (if available at MAVERIC). The REPORT procedure will be used to produce all tables and listings whenever possible. The GPLOT and/or GCHART procedure will be used to produce all figures whenever possible. All statistical appendices (supportive SAS output) will be output directly from the appropriate SAS procedure.

All tables, listings, and statistical appendices will be produced to landscape orientation and will be incorporated into a Word 2003 document (margins: top 1.5”, left, right and bottom 1”) using Courier New 9pt font.

Tables, listings, and figures will be arranged in the order that they appear in the textual sections of this analysis plan, i.e., disposition first, followed by baseline summaries, efficacy summaries, and safety summaries.
All recorded data will be listed following the order and structure of the CRF. In addition, selected derived data used in the analyses will be listed. The listings will include all enrolled subjects (with data relevant to the particular listing) and will be ordered by center, subject, and visit.

6.0 Lists of Tables, Figures and Listings

A. Subject Disposition

Table A1. Recruitment, by Site
Listing A1. Protocol Deviations
Listing A2. Enrollment Waivers
Listing A3. Termination of Study Protocol
Tables A2. Form Completion Status
  a. Baseline Forms Completion, Overall
  b. Follow-up Forms Completion, Overall
  c. Baseline Forms Completion, by Site
  d. Follow-up Forms Completion, by Site

Baseline Characteristics

Table B1. Demographic Characteristics+
Table B2. Lifetime Occupational Sun Exposure and Sensitivity History
Tables B3. Baseline Medical History
  a. Baseline Medical History
  b. Baseline Medical History: Concomitant Medication
Table B4. Skin Disease History at Baseline
Table B5. Previous Skin Cancer Pathology
Table B6. Count of Actinic Keratoses, Full Body Exam
Table B7. Study Medication Use
Table B8. Symptom Assessment during the First 4 Weeks of the Intervention Period
Table B9. Follow-up Assessment at 6 Months
Table B10. Follow-up Assessment of Interval Medical History at 6 Months

Efficacy

Table C1. Biopsy Information
Table C3. KC Treatment Information

Safety

Table D1. Total Non-Serious Adverse Events (NAEs) and Serious Adverse Events (SAEs)
Table D2. Total Non-Serious Adverse Events (NAEs) and Serious Adverse Events (SAEs), by Site
Table D3. Non-Serious Adverse Events (NAEs) by System Organ Class (SOC) and Preferred Term (PT)-Excluding Serious Adverse Events (SAEs)
Title: Statistical Analysis Plan (SAP)

Table D4. Serious Adverse Events (SAEs) by System Organ Class (SOC) and Preferred Term (PT)
Table D5. Non-Serious Adverse Events (NAEs) and Serious Adverse Events (SAEs) by Attributable Event Class
7.0 Subject Disposition Shells