CONFIDENTIAL

Sodium Valproate for the Epigenetic Reprogramming of High-Risk Oral Epithelial Dysplasia

Study Sponsor

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Study Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

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General Information

This document describes the SAVER trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Cancer Research UK Liverpool Cancer Trials Unit (LCTU)) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via LCTU.

Statement of Compliance

This study is designed to comply with the guideline developed by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, LCTU Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004.

UK Registration

This study will have Health Research Authority (HRA) Approval and hold a Clinical Trials Authorisation issued by the Medicines and Healthcare Products Regulatory Agency (MHRA). All research sites will confirm capacity and capability to conduct the study and will sign a Research Site Agreement.

Each centre outside of England must also undergo Site Specific Assessment by the relevant Trust Research and Development department (or Local Research Ethics Committee for Non-NHS Sites) and NHS sites must be granted Research and Development Approval from each Trust where the trial will be carried out.

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Table of Contents

Glossary

AE	Adverse Event
AI	Allelic Imbalance
AR	Adverse Reaction
BMI	Body Mass Index
CI	Chief Investigator
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTU	Clinical Trials Unit
DNA	Deoxyribonucleic acid
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
H&N	Head & Neck
HDACi	Histone de-acetylase inhibitors
HNSCC	Head and Neck Squamous-cell Carcinoma
HTA	Health Technology Assessment
IB	Investigator's Brochure
ICH GCP	International Conference on Harmonisation-Good Clinical Practice
ISDMC	Independent Safety and Data Monitoring Committee
ISRCTN	International Standard Registered Clinical Study Number
IEC	Independent Ethical Committee
IMP	Investigational Medicinal Product
ITT	Intention to treat
LCTU	Liverpool Cancer Trials Unit
LAEP	Liverpool Adverse Events Profile
LREC	Local Research Ethics Committee
MAO inhibitors	Monoamine oxidase inhibitors
MCRN CTU	Medicines for Children Clinical Trials Unit
MHRA	Medicines & Healthcare products Regulatory Agency
MREC	Multi-centre Research Ethics Committee
OED	Oral Epithelial Dysplasia
OSCC	Oral Squamous Cell Carcinoma
PI	Principal Investigator
PIS	Patient Information Sheet
R&D	Research & Development
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SPC / SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV	Sodium Valproate
TARDIS	Treatment Allocation RanDomIsation System
TC	Trial Coordinator
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

1 PROTOCOL SUMMARY

Title: SAVER (Sodium Valproate for Epigenetic Reprogramming in the Management of High Risk Oral Epithelial Dysplasia) is a randomised, double blind, placebo controlled clinical trial with embedded mechanistic and feasibility studies.

Phase: 2

Sample Size: 110 patients

***Main* Inclusion Criteria (for specific detail, refer to section 5):**

- Recently diagnosed oral epithelial dysplasia with a high risk of malignant transformation

***Main* Exclusion Criteria (for specific detail, refer to section 5):**

- Recent or active malignancy either in or outside head and neck region
- Systemic disorders increasing the risk of OSCC
- Oral Lichen Planus
- Chronic previous or current use of Sodium Valproate, or a diagnosis of epilepsy requiring treatment
- Known relative or absolute contraindications to Sodium Valproate (as listed in British National Formulary)

Number of Sites: Approximately 10 research sites.

Study Duration: The trial duration is 6 months per subject, but additional data on malignant transformation will be recorded at the end of trial.

Description of Agent/ Intervention: **Treatment Arm:** Oral sodium valproate 1000mg/day
500mg twice daily. Intervention given for 4 months; including 'step-up' phase for the first 2 weeks, at 500mg once daily.

Control Arm: Matched placebo

Objectives: The aim of this phase II trial is to investigate the effects of sodium valproate as epigenetic chemopreventive therapy on high risk oral dysplasia. In particular, we will establish: clinical activity, mechanism of action and, feasibility of conducting such research in the NHS, in order to inform a decision on a larger phase III trial.

Primary: Clinical activity, measured using the commonly used surrogate end point comprising a composite of

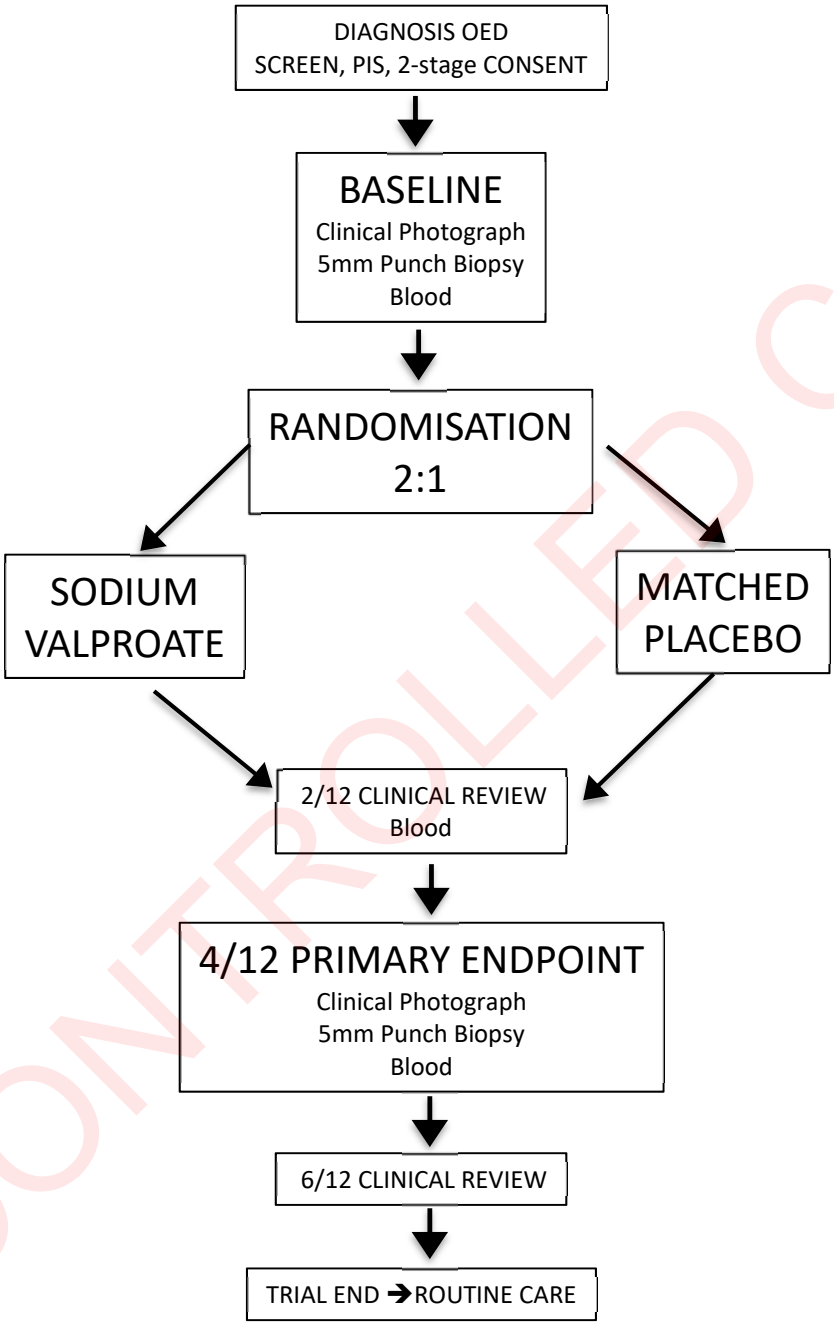
- changes in lesion size,
- histological grade, and
- allelic imbalance

Secondary:

- WHO grade of OED in trial biopsies, and also within the entire resection specimen (where any oral resection is performed within trial period)
- Histopathological evidence of malignant transformation (OSCC) in index lesion or other H&N site within the 6 month 'on-trial' window, and, separately,
- Histopathological evidence of malignant transformation (OSCC) in index lesion or other H&N site within the total period of time that SAVER remains open.
- Feasibility of the trial, defined by:
    - the rate of recruitment per centre,
    - the rate of recruitment for the trial as a whole,
    - compliance with treatment
    - drop-out
- Mechanistic endpoints: i.e. define the changes in gene expression and epigenetic markers, at both tissue specific and systemic level, accompanying sodium valproate monotherapy.
- Qualitative endpoints: an embedded qualitative interview study to systematically investigate patients' experiences of recruitment and participation in the trial

Protocol Summary - continued

Schematic of Study Design:



2 BACKGROUND INFORMATION

2.1 Introduction

There are currently no trials reported or in progress that are designed to explore the role of Sodium Valproate (SV) or valproic acid in chemoprevention of oral squamous cell carcinoma (OSCC).

Systematic reviews in oral cancer chemoprevention. The 2015 Cochrane Collaboration review, "Interventions for treating oral leukoplakia" analysed data from 16 studies and 1002 patients(1). Most of the interventions tested were systemic or topical chemoprevention agents and most were phase II RCTs. Although some did induce resolution of lesions, none of these agents has yet been demonstrated to be effective in preventing transformation to OSCC. These studies demonstrate a gradual convergence in some aspects of trial design, such as choice of primary endpoint, and indicate an estimated drop-out rate of 10%. Other reviews have focused on the complexities of deriving valid primary endpoints for such studies(2), concluding that surrogate endpoints are unavoidable in early phase studies owing to the low frequency and latency of malignant transformation. An ideal strategy is proposed to incorporate molecular markers that are pharmacologically targeted by nontoxic drugs and are known to actively participate in carcinogenesis.

Reviews of the role of histone de-acetylase inhibitors (HDACi) & SV in field of oncology. HDACis are an emerging class of drugs that have shown promise as anticancer agents when used alone or in combination with conventional therapies. HDACi and SV have been comprehensively reviewed in their role in combination therapies, with either cytotoxic chemotherapy or targeted agents, in haematological malignancy or recurrent / metastatic solid tumours(3, 4). There is good evidence for clinical benefit of epigenetic therapy with other more toxic agents in some haematological precancers and cancers (e.g. myelodysplastic syndromes/ myelocytic leukaemia). In contrast, the rationale for HDACi monotherapy in the setting of chemoprevention presents a differing opportunity, but there is a relative paucity of data. While tumours of hematopoietic origin and selected solid tumours may undergo differentiation following SV exposure, for most solid tumours the primary effect is a reversible cytostatic response(5). One hypothesis is that this may indeed be sufficient to prevent transformation in premalignant lesions as a monotherapy. At first it may appear unlikely that a pure epigenetic therapy could realistically prevent OSCC which is characterised by widespread copy number alterations(6), a significant number of genetic mutations(7) and degree of genomic instability. However, the co-existence and interdependence of genetic and epigenetic aberrations is only recently becoming apparent. There are key epigenetic drivers of DNA integrity and repair (such as MGMT,hMLH1, ATM. FANC pathway) that may well be valid targets in preventing genetic progression of premalignant lesions.

Pre-clinical studies of HDACi. In vitro and various animal model studies point to a role for HDACi in the induction of tumour specific, selective, engagement of proapoptotic(3) and cell proliferation pathways(8) in a variety of tumour types. Further studies(9) suggest valproic acid targets DNMT1 (DNA methylation machinery) in smoke induced aerodigestive malignancy, indicating that effects on DNA promoter methylation of tumour suppressor genes may be both direct, as well as via effects on HDAC. OSCC has been shown to be significantly driven by promoter methylation across a variety of critical tumour suppressor genes(10, 11) which highlights the therapeutic potential role of this approach. There is evidence that epigenetic events are critical to the malignant progression pathway for OED/OSCC. Several genes show promoter methylation in transforming OED, with p16 convincingly predictive of eventual OSCC(12). MGMT, DCC, EDNRB & CYCA1 methylation(13) also distinguish OED from OSCC, suggesting that epigenetic events are indeed central to the earlier steps in pathogenesis of OSCC.

Clinical and preclinical evidence for HDACi / SV in OSCC. Of the 70 SV trials listed on clinicaltrials.gov carried out in the setting of cancer, only 4 include H&N cancers (2 thyroid, 1 nasopharynx, 1 adjuvant chemoradiotherapy) but none as monotherapy and none in the preventive setting. It has been reported recently that histone deacetylase inhibitors (HDACIs) can block the growth of OSCC cell lines by reversing the silencing of the tumor suppressor genes. Suberoylanilide hydroxamic acid (SAHA) suppressed the in vitro proliferation of OSCC cell lines in a dose and time-dependent manner, leading to G1 phase cell-cycle arrest and a decrease in the percentage of S-phase cells(14). The same authors observed that the growth of xenograft tumours in nude mice was significantly blocked by the administration of HDACi. In another in-vitro study(15), a novel HDACi (S-HDAC42) mediated caspase-dependent apoptosis in a panel of oral squamous carcinoma cell lines. The mechanism was through targeting multiple signaling pathways relevant to cell cycle progression and survival, influencing downregulation of phospho-Akt, cyclin D1, and cyclin-dependent kinase 6, accompanied by increased p27 and p21 expression. There is also some in-vitro evidence(16) that valproate causes a dose-dependent increase in histone H3 acetylation and p21 expression, as well as dose-dependent cytostasis in OSCC.

Additionally, the combination of a clinically achievable concentration of valproate plus cisplatin caused a 3x to 7x increase in cisplatin cytotoxicity in vitro, which was specific to SCC and not shown in keratinocytes. The response to valproate was also observed in tumour biopsy samples collected from patients prior to and following a 1 week low to medium dose oral course (600mg bd).

The Kang study(17) comprises follow up of 440,000 patients in the US VA (Veterans' Affairs) System, with long term psychiatric or neurological diagnoses and at high risk of cancer. There was a lower incidence of head and neck malignancy in the group using SV (HR 0.68, 95% CI , 0.50-0.93). The reduction in risk was maintained in a multivariate analysis for age, sex, race, smoking, psychiatric or neurological disease, COPD, alcohol and substance use (HR 0.66, CI, 0.48-0.92). The weight of this observation is reinforced by dose effect; with both length of treatment and dose of SV correlating with a further reduction of risk. The most plausible mechanism of reduction of cancer risk is through the epigenetic effects of SV through HDAC inhibition.

2.2 Rationale

The incidence of OSCC has risen sharply over recent decades and results in high mortality and morbidity. Despite calls for prevention and early diagnosis, currently there are no NIHR portfolio studies addressing the OED-OSCC continuum. Most OSCC is preceded by premalignant lesions which may be clinically apparent, but for those lesions there is an unmet need in effective treatment options. The commonest treatment offered is surveillance or surgery, neither have strong evidence to support nor address the underlying pathogenesis. Many patients have lesions in the absence of identifiable risk factors such as smoking, and indeed such idiopathic lesions have higher malignant transformation rates, approaching 30%(19). New data demonstrating a reduction in incidence of HNSCC associated with long-term SV, the plausibility of epigenetic mechanisms underlying this, and clinical need underline the need for this trial. The resultant clinical, mechanistic and feasibility data will inform the decision for a later larger phase III trial with cancer endpoints necessitating much larger cohorts and longer follow-up.

2.3 Objectives

The aim of this phase II trial is to investigate the effects of sodium valproate as epigenetic chemopreventive therapy on high risk oral dysplasia. In particular, we will establish: clinical activity, mechanism of action and, feasibility of conducting such research in the NHS, in order to inform a decision on a larger phase III trial.

Clinical activity of SV as a chemopreventive therapy in individuals with high-risk oral epithelial dysplasia. We will establish clinical activity using a surrogate endpoint that has been commonly used in comparable trials(20-22). This endpoint is a composite of clinical, pathological and molecular changes seen before and after treatment with study drug. We will recruit patients who have index lesions amenable to longitudinal clinical assessment with a high risk of malignant transformation. This design will enable a relatively early assessment (4 months) of clinical activity within the context of a relatively small clinical trial with limited follow-up.

Induction of epigenetic reprogramming, gene expression, transcription senescence, proliferation and apoptotic pathways. SV has a known mechanism of action as a histone de-acetylase inhibitor . The reduced risk of head and neck cancers demonstrated in patients taking SV has been hypothesised to be through epigenetic reprogramming of premalignant lesions(17). Here, we will assess, from paired biopsies of oral lesions, i.e. before and after study drug: tissue-specific epigenetic changes, changes in gene expression, expressed markers of proliferation, apoptosis and senescence. We will also assess pharmacodynamic biomarkers of histone acetylation in circulating white cell DNA. The presence of a placebo control will enable us to determine whether these effects are specific to SV.

Feasibility & acceptability of larger randomised chemoprevention trial. Progression of the trial will be dependent on predetermined recruitment data within the centres, for which stopping criteria will be set. Further, embedded qualitative research using interviews will inform how patients view this trial, and whether a similar larger phase III trial could be attempted in the UK. Further, we will assess toxicity and tolerability of SV specifically in this setting.

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

Toxicity of Sodium Valproate. SV at 1000mg/day is associated with mild or absent toxicities, and is well tolerated(18). Higher doses, sometimes justified in epilepsy, are associated with weight gain, tremor, drowsiness and cognitive slowing. The normal dose range used in neurology practice is 1000-2000mg/ day with a maximum of 2500mg. In the context of premalignant H&N conditions, we feel that these would not be justified. The impact of weight gain will be reduced by excluding obese patients and teratogenic effects will be avoided by excluding women of childbearing age.

Potential risks of delay to therapy (in those patients listed for surgical excision). An interim study visit at 2 months will mitigate any risk that lesions might undergo malignant transformation in the 4 month experimental window. This will allow clinical assessment of oral lesions and further to facilitate collection of toxicity / AE (Adverse Events) data. In total, SAVER patients will be clinically examined 5 times in the 6 month study, each time signs of malignant transformation will be sought and acted upon.

2.4.2 Known Potential Benefits

Potential benefit to individual – Surgery is not always possible for all lesions or all patients, and recurrence rates for premalignant lesions are high. Localised therapies fail to treat the wider field, often encompassing the entire upper aerodigestive tract, and therefore do not address the risk of multifocal lesions. The limitations of current treatments underscore the need for systemic agents in this setting(2).

Societal benefit. There is no robust evidence that current standard therapy for OED is effective in reducing the risk of OSCC development. With more effective treatment of OED it should be possible to reduce the incidence of oral cancer, of evident benefit not only from the perspective of improved public health but also reduce the NHS costs associated with treatment. A recent HTA (Health Technology Assessment) study estimated the total costs over a 3 year period as: precancer £1869, OSCC stage I £4914, stage II £8535, stage III £11,883 & stage IV £13,513. If even a proportion of the 6,500 new cases of OSCC could be halted at the stage of OED, it can be seen that very substantial savings are theoretically possible, in addition to the morbidity, loss of life and functional impact.

3 SELECTION OF CENTRES/CLINICIANS

Centres will be selected on their clinical caseload of oral epithelial dysplasia and willingness to enter into trial contracts with the sponsor.

3.1 Centre/Clinician Inclusion Criteria

a. Positive Capacity and Capability Assessment by Research and Development (R&D) Department
b. Approval by MHRA
c. Completed Research Site Agreement
d. Completion and return of 'Signature and Delegation Log' to LCTU

3.2 Centre/Clinician Exclusion Criteria

Those centres who do not fulfil the above inclusion criteria will not be permitted to participate in the trial.

4 TRIAL DESIGN

4.1 Overall Design

SAVER is a phase II clinical trial with embedded mechanistic and feasibility studies. It is randomized, double blind and placebo controlled with a planned recruitment of 110 patients. The randomisation is in the ratio 2 SV (73 patients) :1 placebo (37 patients). The study population includes patients with premalignant oral lesions that have a histological diagnosis of oral epithelial dysplasia (OED) and are at high risk (considered to be at least 20% over 5 years of malignant transformation).

4.2 Primary Endpoint

The primary endpoint is a measure of clinical activity and a surrogate – it is a composite of clinical, pathology and molecular lesional changes which has been previously used, with peer review, in randomised trials, within the same field(20). It is derived from clinical measurement, photographs and punch biopsy tissue comparing baseline to primary endpoint (4 months).

Timing of primary endpoint: The primary endpoint is 4 months from the date of commencement of study drug. A variance from this time point is allowed for pragmatism, such that a window of:

2 weeks (14 days) prior
4 weeks (28 days) following

is acceptable.

(similar variance in timing of 2 month, and 6 month study visits are also applied)

The primary endpoint is expressed as a score:

Lesional size responsiveness score (on scale -3 to +3 as below) + Histologic grade responsiveness score (Pre – Post-treatment grade) + LOH responsiveness score (Pretreatment– Post-treatment events).

The assignment of scores in these various components is described in appendices as below.

Finally, overall therapeutic responsiveness for each lesion is then categorized:

Regressed* : ≥1,
Stable : <1 and >-1,
Progressed : ≤1

(* High responder ≥4, Intermediate responder =3, Low responder =1 or 2.)

4.3 Secondary Endpoint(s)

- WHO grade of OED in trial biopsies, and also within the entire resection specimen (where any oral resection is performed within trial period)
- Histopathological evidence of malignant transformation (OSCC) in index lesion or other H&N site within the 6 month 'on-trial' window, and, separately, within the total period of time that SAVER remains open.

- Feasibility of the trial, defined by:
    - the rate of recruitment per centre,
    - the rate of recruitment for the trial as a whole,
    - compliance with treatment
    - drop-out
- Mechanistic endpoints: i.e. define the changes in gene expression and epigenetic marks, at both tissue specific and systemic level, accompanying sodium valproate monotherapy.
- Qualitative endpoints: an embedded qualitative interview study to systematically investigate patients' experiences of recruitment and participation in the trial

5 STUDY POPULATION

5.1 Inclusion Criteria

1. Recent (<12 months) histological diagnosis of confirmation of OED according to the World Health Organisation (WHO) criteria (i.e: Patients may be eligible who have a longstanding diagnosis of OED diagnosis but then would need either a recent biopsy (<12months) or to enter the screening route to randomization)
2. Index lesion* which must be:
    a. Accessible
    b. Measurable
    c. Amenable to clinical photography
    d. Oral cavity, lip or oropharynx
    e. Minimum lesion size: 10mm x 10mm, or >=100mm^2

    (* other 'non-index' lesions in the same patient may be present and do not make the patient ineligible)
3. Treatment plan for either surgical resection, or for surveillance of the lesion by means of clinical and photographic follow-up.
4. The index lesion must be considered to be deemed at high risk (i.e. estimated >20% over 5 years) of malignant transformation, i.e.:
    a. WHO severe OED or
    b. WHO mild or moderate OED, with at least one additional high risk feature(s) from the list below:
        i. non-smoker (less than 100 cigarettes or equivalent over whole lifetime)
        ii. lesion size >200mm^2
        iii. lateral tongue site
        iv. mucosal speckling or heterogeneous appearance
        v. excised OSCC during previous 5 years (but not within previous 6 months).
5. The patient is fully informed, has received PIS (Patient Information Sheet) & considered during a 'cooling-off' period, is competent to consent, age >=18, and is able to comply with minimum attendance requirements.

5.2 Exclusion Criteria

1. Synchronous or metachronous OSCC (i.e. at time of screening or within 6 months)
2. Active malignancy outside head and neck region (with exception of non-melanoma skin cancer)
3. Inflammatory co-existing oral lesions: lichen planus, fungal (candidiasis) oral lesions, scleroderma
4. OSCC susceptible conditions e.g. Fanconi Anaemia, Blooms syndrome, Ataxia Telangectasia, Li Fraumeni syndrome etc.
5. Clinical and/or histopathological diagnosis of oral submucous fibrosis
6. Immunosupression, however, low dose i.e. <10mg/day prednisolone, or equivalent steroid, (as per BNF conversion table), are not considered an exclusion.
7. Chronic previous or current use of Sodium Valproate
8. Diagnosed epilepsy that has chronic previous or current use of *any* antiepileptic therapy
9. Obesity (Body Mass Index >= 30)
10. Known relative or absolute contraindications to Sodium Valproate (as listed in British National Formulary), and specifically:
    a. Acute porphyria
    b. Known or suspected mitochondrial disorders

c. Personal or family history of severe hepatic dysfunction, current hepatic dysfunction (as evidenced by LFTs outwith reference range and prolonged prothrombin time)
d. Past history or current pancreatitis
e. Women with child-bearing potential (<2 years post menopause), pregnancy, breast feeding. (This is iterated in more detail in SOP as per appendix 1)
f. Potential drug interactions (particularly antipsychotic and anticonvulsant medications, MAO inhibitors, antidepressants, benzodiazepines), specifically patients taking phenobarbital, primodone, carbopenem antibiotics (imipenem, panipenem, meropenem), cimetidine, erythromycin, lamotrigine, olanzapine, pivmecillinam, sodium oxybate, zidovudine, carbamazepine, phenytoin, rifampicin, salicylates e.g. aspirin.
g. Patients with suicidal ideation and behaviour should be excluded from the trial. Patients should also be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered.
h. Patients with known or suspected mitochondrial disease, systemic lupus erythematosus or hyperammonaemia

5.3 Patient Transfer and Withdrawal

In consenting to the trial, patients are consenting to trial treatment, follow-up and data collection. If voluntary withdrawal occurs, the patient should be asked to allow continuation of scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the subject's condition becomes stable.

5.3.1 Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient or for follow-up via GP.

A copy of the patient CRFs should be provided to the new site. The patient will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre. The LCTU should be notified in writing of patient transfers.

5.3.2 Withdrawal from Trial Intervention

Patients may be withdrawn from treatment for any of the following reasons:

a. **Development of OSCC**.

The initial research biopsy will be evaluated by central pathology review within 2 weeks to exclude invasive OSCC at baseline. If invasive OSCC is seen on this biopsy, this will be immediately fed back, synchronously to both the research site and SAVER trial management team. The patient would be excluded from the SAVER trial.

If at any stage of the trial (either at or in between study visits, or subsequently after trial window has closed for that patient but during the period when the trial remains open) there is a clinical suspicion of malignant transformation, a biopsy will be performed. This will be sent to, and interpreted by, the trial pathologist at Newcastle University. This biopsy will also be carried out as per the trial diagnostic biopsies using a 5mm punch biopsy accompanied by a specific CRF request form. If the biopsy demonstrates invasive OSCC, the patient ceases study drug, is recorded as showing malignant transformation and returns to normal clinical management and follow-up i.e. standard

of care through the respective head & neck oncology multidisciplinary team. If histopathology does not support a diagnosis of OSCC, the patient returns to normal study schedule or normal standard of care.

b. **Unacceptable toxicity.** Treatment may be discontinued for any toxicity with a significant impact on quality of life (generally grade 2 or higher, however persistent grade 1 AEs may also lead to discontinuation). A 50% dose reduction (500mg/day) may also be considered for persistent grade 1 toxicities rather than withdrawal from trial, and this will normally be possible without unblinding the trial but after discussion with the CI. Patients discontinuing due to toxicity will not be unblinded apart from in the event of a suspected unexpected serious adverse event (SUSAR), and will be followed up and assessed as per protocol.

c. **Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion**.

If a patient wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up (see section 5.3.3).

5.3.3 Withdrawal from Trial Completely

Patients who withdraw from the trial for other reasons have previously consented to follow-up in the trial. Data up to this time can be included in the trial if anonymised. They may need to reaffirm that they consent to follow-up through usual NHS mechanisms. If the patient explicitly states their wish not to contribute further data to the study, a withdrawal CRF should be completed.

6 ENROLMENT AND RANDOMISATION

6.1 Screening

Potentially suitable patients will be screened for eligibility for the SAVER trial using the screening log provided via the LCTU portal www.lctu.org.uk. Patients may be eligible who have longstanding OED provided inclusion criteria have been met, in particular that they have had a biopsy demonstrating the appropriate diagnosis within the 12 months preceeding the date of randomisation.

SAVER also provides an optional two stage screening & consent process for patients who have a lesion where biopsy is clinically indicated, but a diagnosis of high risk OED has not yet been made. The patient will be provided with a shortened 'screening' information sheet and consent form such that the diagnostic biopsy, in the event that it meets the criteria, will also fulfil the criteria for baseline tissue for the SAVER trial. This will potentially avoid the situation where a patient is offered a 'research only' biopsy almost immediately after a 'diagnostic' biopsy as the only means to enter the trial. In this circumstance, the biopsy is processed outwith the centre using the SAVER pathology central review. If the diagnosis offered is not consistent with eligibility for the trial, the report and tissue are returned to the recruiting centre. If the diagnosis made is consistent with inclusion to the SAVER trial, the patient is then offered full patient information and consent process.

6.2 Enrolment/ Baseline

Trial specific screening activities will only be performed after patients have consented to trial participation and signed the informed consent form.

Randomisation must be carried out within 90 days of the research biopsy report, and commencement of trial treatment within 30 days of the date of randomisation.

Other assessments can only be used for screening if performed within 90 days prior to the first dose of treatment (with the exception of histology showing OED which, as clarified above, must be within 12 months)

The following screening assessments should be performed:

b. Written Informed Consent
c. Assessment of eligibility criteria
d. Review of medical history
e. Review of concomitant medications
f. BMI examination
g. Oral examination
h. Lesion measurement (with clinical photographs and ruler)
i. Haematology / clinical chemistry
j. EDTA blood sample for PWBC (to GCLP standard)
k. Research biopsy (split between GCLP & Path labs)

Patients who have given informed consent and have been found to comply with all inclusion and exclusion criteria will be enrolled on to the trial by the LCTU

Importantly, no patient may be randomised to the trial prior to having a definitive SAVER pathology report from the central pathology laboratory in Newcastle.

RANDOMISATIONS CONTACT DETAILS:

SAVER Trial Coordinator

Tel: 0151 795 7328 (Mon- Fri 09.00 – 17.00) – General Enquires

Fax 0151 794 8931 – Randomisations

7 TRIAL TREATMENT/S

7.1 Introduction

Patients will be randomised between Sodium Valproate (arm A) and matched placebo (arm B) in the ratio 2:1.

7.2 Arm A

7.2.1 Formulation, Packaging, Labelling, Storage and Stability

Sodium valproate is an anticonvulsant.

Formulation	Lilac coloured circular biconvex tablet (500mg, enteric coated tablets)
Active Ingredient Name	Sodium valproate
Excipients	For a full list of excipients, see section 6.1 of the SmPC
Prolonged release	No
Pack Size	Epilim 500 Gastro-resistant tablets are supplied in blister packs further packed into a cardboard carton. Pack sizes of 170 and 120 tablets.
Manufacturer's name	Sanofi
Suppliers name	Catalent
Storage	Epilim is hygroscopic. The tablets should not be removed from their foil until immediately before they are taken. Where possible, blister strips should not be cut. Store in a dry place below 30°C.

Sodium valproate/placebo are IMP's and are over labelled stock according to Annex 13 requirements of EU GMP.

Oral sodium valproate tablets, 1000mg/day (500mg twice daily).
Intervention given for 4 months; including 'step-up' phase x 2 weeks, at 500mg once daily

Pharmacy will not need to do any re-labelling of the Sodium valproate / placebo. All study drugs will be provided to sites in labelled packs which will be blinded, once the site has been activated by the Liverpool Cancer Trials Unit.

The material will arrive at site ready to be dispensed to patients, local Pharmacy will need to confirm shipment of the drug to the site.

When a patient is randomised by staff at the LCTU, kit/pack number(s) to be dispensed to the patient will be allocated and an email sent to the site confirming these details.

All investigator products must be kept in a secure place appropriate storage conditions. A description of the appropriate storage and shipment conditions is specified on the investigational product label.

The stored study drug supplies must be accessible to authorized staff only. The storage area must also have adequate control of temperature in order to maintain stability and potency of study drug supplies. The tablets should be stored in the original pack until use. For further information, investigators should refer to the investigational product label.

Please see the pharmacy manual for further details of initial supply and re-supply of Sodium Valproate and/or placebo for the trial.

An example SmPC is available here http://emc.medicines.org.uk/ .

7.2.2 Prescribing and distribution of Sodium valproate

Investigational products may only be prescribed to a trial patient by the principal investigator or sub investigator named in the study delegation log.

Research site pharmacies must maintain a drug accountability log, template logs will be provided by the LCTU; however sites may use their own provided they have been approved by the study team.

A copy of the Sodium valproate prescription must be retained with the drug accountability log. A template prescription will be provided by the LCTU; however sites may use their own provided it has been approved by the study team.

7.2.3 Preparation, Dosage and Administration of Sodium valproate

Sodium valproate will initially be taken orally for 14 days at a dose of 500mg once daily.

From day 15 until 4 calendar months after day 1, sodium valproate will be taken orally continuously at a dose of 500mg twice daily.

Tablets should be taken with or after food. If a dose is delayed by more than 4 hours, the dose should be omitted. In the event of vomiting, a 'replacement' tablet should not be taken, but dosing may resume as normal at the next scheduled time.

7.2.4 Dose Modifications

No dose modifications are permitted during the SAVER trial, as the sodium valproate dose is low to medium and expected to be well tolerated. Treatment may be discontinued for any toxicity with a significant impact on quality of life (generally grade 2 or higher, however persistent grade 1 AEs may also lead to discontinuation). Patients discontinuing due to toxicity will not be unblinded apart from in the event of a suspected unexpected serious adverse event (SUSAR), and will be followed up and assessed as per protocol.

7.3 Arm B

The placebo will be composed of suitable pharmaceutical excipients and will match the colour of Epilim. Patients on placebo should be treated as if on sodium valproate unless in a medical emergency when the unblinding procedure should be followed.

Blinding and Unblinding:

SAVER is set-up as a double blind trial. Patients, Investigators, site staff (with the exception of Pharmacy) and the SAVER trial team (with the exception of Trial Statistician, an LCTU IT representative, Monitors and unblinded Trial Coordinators) will remain blinded with regard to the randomised treatment allocations.

Blinding for the SAVER trial will be performed and maintained through the TARDIS system.

The treatment allocation must not be unblinded except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment randomisation, or for the submission of SUSAR reports.

7.4 Accountability Procedures for Study Treatment/s

The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug.

All study drugs must be accounted for, including study drug accidentally or deliberately destroyed.

All discrepancies between amounts of study drug dispensed and amounts returned must be documented.

Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol without prior approval.

If appropriate, drug storage, drug dispensing, and drug accountability should be delegated to the pharmacy section of the investigative site.

Any remaining Sodium valproate / placebo tablets must be kept for inspection by the LCTU if required and shall only be destroyed with the written permission of the LCTU.

Assessment of Compliance with Study Treatment/s

All patients will have plasma valproate assessment at 2 months and 4 months, however this will be blinded to site investigators and only available retrospectively after locking of the trial data.

In order to confirm compliance with sodium valproate and placebo administration, patients' will be given a diary sheet to be completed each day. Research Nurses will collect the unused tablets and completed diary cards and record any circumstances of non-compliance in the patient notes and on the CRF. The returned medication should be sent to the site pharmacy for storage.

Any remaining Sodium valproate / placebo tablets must be kept for inspection by the LCTU if required and shall only be destroyed with the written permission of the LCTU.

7.5 Concomitant Medications/Treatments

7.5.1 Overdose

Sodium valproate overdose resulting in plasma concentrations up to 5 to 6 times the maximum therapeutic levels for seizures (i.e. 15-20 times the dose used in SAVER) are likely to result in nausea, vomiting and dizziness only.

In cases of massive overdose (10 to 20 times the maximum therapeutic levels for seizures) signs include CNS depression, coma, muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidoisis. A favourable outcome is usual although deaths have been reported. Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring, consideration of gastric lavage up to 10-12 hours following ingestion, haemaodialysis and haemoperfusion.

7.5.2 Medications Not Permitted

The following drugs interact with sodium valproate. Patients prescribed these drugs are therefore ineligible for the SAVER trial:

Antipsychotic and anticonvulsant medications,

MAO inhibitors,

Antidepressants,

Benzodiazepines

Also: phenobarbital, primodone, carbapenem antibiotics (imipenem, panipenem, meropenem), cimetidine, erythromycin, lamotrigine, olanzapine, pivmecillinam, sodium oxybate, zidovudine, carbamazepine, phenytoin, rifampicin, salicylates – e.g. aspirin.

7.6 Co-enrolment Guidelines

There are no trials which compete on inclusion criteria with SAVER in the UK or Ireland at the time of writing the protocol.

8 ASSESSMENTS AND PROCEDURES

8.1 Schedule of Trial Procedures

Procedures		Screening	Baseline	Follow-Up Schedule: 2^ months	4^ months	6^ months	Within 6 months of trial end
Signed Consent Form		X	X				
Assessment of Eligibility Criteria		X	X				
Review of Medical History		X	X				
Review of Concomitant Medications		X	X	X	X	X	
Verbal Consent (Information Study contact)		X					
Study Intervention (0-4 months)			X	X	X		
Risk exposure update (smoking and alcohol)		X	X	X	X	x	
Examination	Body Mass Index	X					
	Oral Examination	X	X	X	X	X	
	Lesion Measurement with Clinical Photograph & ruler		X		X		
Assessment of Adverse Events (LAEP Questionnaire – Appendix 3)				X	X	X	
Clinical Laboratory^	LFTs & PT/APPT		X	X	X		
	Haematology: FBC		X	X	X		
Research Blood	EDTA sample for PWBC (The first of which to GCLP standard for subsequent AI studies)		X	X	X*		
	Plasma Sodium Valproate levels			X	X*		
Research Biopsy	Formalin-fixed paraffin-embedded 5mm punch biopsy		X		X*		
Dispense study drugs: Epilim/Placebo			X	X			
Establish if new diagnosis of OSCC from case note review via telephone.							X

*The patient must take their allocated study drug right up to, **and including**, the day of their 4-month biopsy.

^Within a tolerated 'window' of 2 weeks prior, and 4 weeks following, & related to date of commencement of study drug

8.2 Procedures for assessing Efficacy

Efficacy is assessed by determining changes between baseline and 4 months in the primary endpoint.

The primary endpoint is a measure of clinical activity and a surrogate – it is a composite of clinical, pathology and molecular lesional changes which has been previously used, with peer review, in randomised trials, within the same field(20). It is derived from clinical measurement, photographs and punch biopsy tissue comparing baseline to primary endpoint (4 months).

The primary endpoint is expressed as a score:
Lesional size responsiveness score (on scale -3 to +3 as below) + Histologic grade responsiveness score (Pre – Post-treatment grade) + LOH responsiveness score (Pretreatment– Post-treatment events).

Finally, overall therapeutic responsiveness for each lesion is then categorized:

Regressed* : ≥1, Stable : <1 and >-1, Progressed : ≤-1
(* High responder ≥4, Intermediate responder =3, Low responder =1 or 2.)

Assessment of lesional size responsiveness score: A -3 to 3 responsiveness score scale of lesion size (maximum mucosal dimension in mm) from paired, blinded clinical photos with in-site ruler. Commercially available lesion rulers will be used (Puritan© stick - 6" Wound Measurement Device - 1506-PFB DM)

Correlation of size / outcome score:
75% decrease = 3,
50% to 74% decrease = 2,
25% to 49% decrease = 1,
0% to 24% decrease or increase = 0,
25% to 49% increase = -1,
50% to 74% increase = -2,
and =75% increase = -3.

Assessement of histologic grading*:Formalin-fixed paraffin-embedded 5mm punch biopsy, bisected and stained with hematoxylin and eosinn.

Photomicrographs taken with 10x objective lens and digital camera will facilitate multiple assessments at remote sites.

***For detail, see pathology SOP (Appendix 2)**

A 0–8 grade scale (independent blinded assessment by 2 Oral Pathologists MR/PS):

0=normal with or without hyperkeratosis
1=atypia with crisply defined clinical margins
2=mild dysplasia
3=mild-moderate dysplasia
4=moderate dysplasia
5=moderate-severe dysplasia
6=severe dysplasia
7=carcinoma in-situ
8=invasive SCC

LOH responsiveness score*:
Tissue will be laser micro-dissected and DNA will be isolated using QIAamp DNA Micro Kit (QIAGEN). DNA will be quantified by nanodrop.

For PCR amplification, forward primers currying 5' fluorescent label and reverse primer bearing a 5' biotin label will be used for the following loci:

3p14 [D3S1007 (VHL), D3S1234 (FHIT)],
9p21 [D9S171, D9S1748 (P16/CDKN2A), D9S1751 (P16)],
9p22 (IFN-a), and 17p13 [D17S786 (P53) and TP53].

The multiplex reaction will utilise QIAGEN Multiplex PCR Kit and will include 200nM of each primer and 20 ng DNA. The thermal profile is: 95°C for 5 min, 25 cycles consisted of 94°C for 30 sec, 55°C for 30 sec, 72°C for 45 sec, and a final extension step at 72°C for 30 min to maximise non-template A addition.

PCR will be cleaned up using High Performance Streptavidin Sepharose beads (GE, UK). Beads will be resuspended in 12 ml high deionised formamide (Lie Technologies) containing 1 microlitre GeneScan 400HD ROX (ThermoFisher Scientific) denatured at 95°C for 2 min and run on a 3500xl Genetic analyser using a 36 cm capillary and POP-7 polymer (ThermoFisher Scientific).
Analysis will be done using the Genemapper software (ThermoFisher Scientific). LOH thresholds have been defined in detail in related studies of target:reference allelic ratios 0.77 / 1.23 (Liloglou et al, Cancer Res 61, 1624–1628, 2001)

*Further details on AI assay, see relevant appendix.

8.3 Procedures for Assessing Safety

Adverse events will be assessed at each trial visit (minimum of 5 appointments over 6 months), as well as at any unscheduled visits. In addition, patients will be provided with instructions to contact the trial team in the event of any toxicity. All patients will have a full blood count, and LFTs performed as outlined in the schedule, to assess for potential haematological and hepatic toxicities. In view of the small theoretical risk of clotting aberrations in association with SV, a clotting screen will be performed prior to surgery.

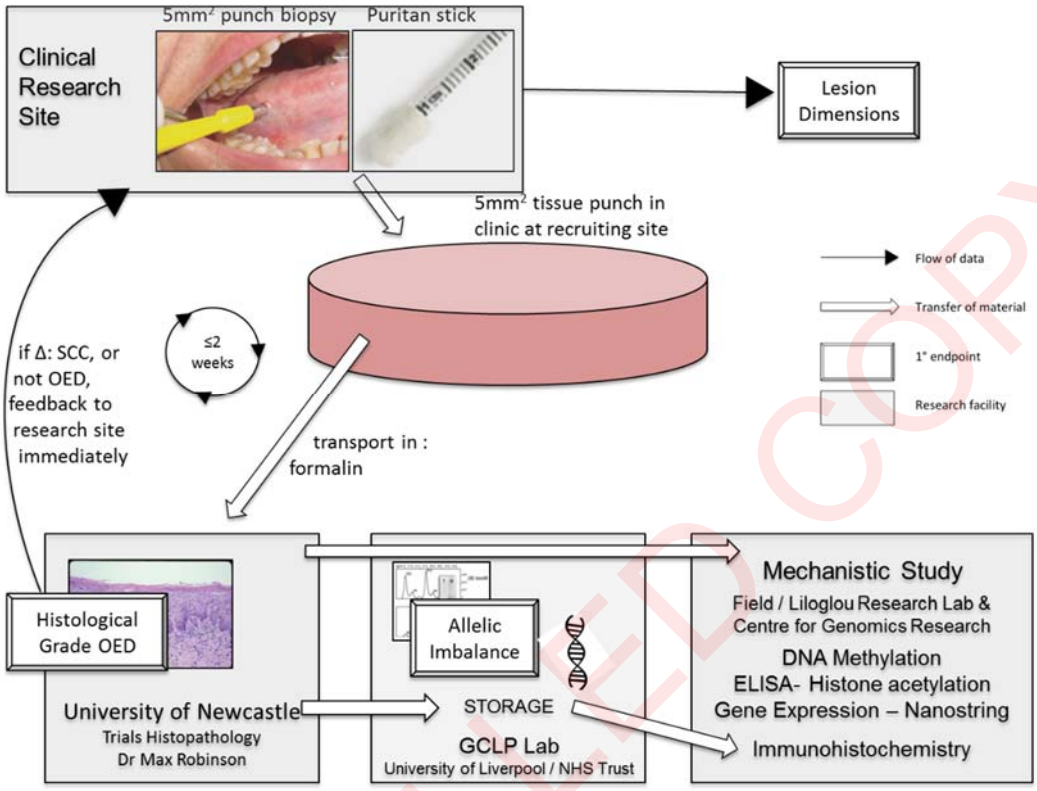
A standard pharmacovigilance programme will be set up. In the event of a SUSAR, the subject will be unblinded, and in the event of the adverse event being judged to be due to SV, this will be reported to the MHRA using the yellow card system. Assessment of AEs associated with sodium valproate will be established using a modified Liverpool Adverse Events Profile (LAEP) questionnaire, which is specifically designed and validated to measure the AE profile of anticonvulsants such as sodium valproate.

8.4 Assessments

8.4.1 Special Assays or Procedures

1. Clinical photos with in-field ruler (provided as a “Puritan Stick”) x 2 per patient. Quality assurance of the photographs is provided by the TMG for the first 5 photographs returned from each site and a random sample of 10% of subsequent returns per annum.

2. Research biopsy (5mm punch biopsy) x 2 per patient. Quality assurance of the tissue returned to both diagnostic lab (University of Newcastle) and GCLP lab (University of Liverpool) is provided by the TMG for the first 5 samples returned from each site and a random sample of 10% of subsequent returns per annum. The division and destiny of tissue from each research biopsy is summarised in the figure below.



3. Plasma sodium valproate assays x 2 per patient (returned to LCTU and research staff retain blinding), and venous blood also for PWBC and analysis for AI, systemic acetylation studies.

8.5 Substudies

There are 2 main substudies within the SAVER trial:

8.5.1 Mechanistic Study

Changes in gene expression and epigenetic marks will be defined, at both tissue specific and systemic level, accompanying sodium valproate monotherapy. Blood & tissue punch biopsy samples will be collected from each patient prior to and following study drug. 5mm punch biopsies will be split: half used for histology and immunohistochemistry (IHC), and half for combined DNA/RNA/protein preparation. It is important that patients remain on their allocated study drug right up to the day of their 4-month biopsy.

8.5.1.1 **Blood samples**: H3K27 & pan-acetylation assays will be conducted in DNA from circulating leukocytes , effectively as a measure of the pharmacodynamic systemic epigenetic activity of SV.

8.5.1.2. **Tissue**: Phenotypic response to SV will be established using ELISA (enzyme-linked immunosorbent assay) for H3K27 and pan-acetylation, & Immunohistocytochemistry for stem cell, apoptotic and senescence markers.

8.5.1.2.1 **DNA:** Promoter methylation associated with malignant progression from OED (P16, DCC, EDNRB) - (Hall et al, Schussel et al.) using in-house pyrosequencing

assays and RTqMSP where these are not optimal.

8.5.1.2.2 **Gene Expression**: Nano-string transcriptional profiling, which will allow us to assess genes of interest including tissue -specific (i.e. OED specific) senescence markers/ HDACi response in cancer tissue. & the Nanosting ("off the shelf") Human Cancer Reference panel.

8.5.1.3. Additional mechanistic studies relevant to the biology of SV effects or progression from OED to OSCC, such as may emerge or become relevant as the trial progresses.

8.5.2. Qualitative Study

8.5.2.1. Overview

The SAVER trial will include an embedded qualitative interview study, called the SAVER Information Study.

8.5.2.2. Introduction

The SAVER Information Study will involve qualitative interviews with patients who have been invited to join the trial to systematically explore patients' experiences of recruitment and participation in SAVER. Qualitative studies have helped to enhance the design of previous trials from the perspective of patients, and improve patients' experience of recruitment and participation(28). The Information Study's findings will be used by clinicians as SAVER is ongoing to inform the recruitment process and communication with patients, and to enhance the patient information materials for SAVER. The aim will be to help patients to make informed decisions about whether to join the trial, and to address any potential recruitment and retention issues. We will also use the Information Study findings to enhance the design and acceptability of any future phase III trial from the perspective of patients.

8.5.2.3. Rationale

SAVER is the first chemoprevention trial to be implemented in this context. It is therefore important to learn from patients with first-hand experience of being invited to join SAVER so that we can optimize its acceptability. We will therefore seek to interview patients who decline SAVER or withdraw from it, as well as those who consent and remain in the trial. Previous embedded qualitative studies have shown the value of accessing the perspectives of patients regardless of whether or not they go on to participate in the trials. We note that other qualitative studies (e.g. RECRUIT- 07/MRE08/60; REFRAMED 11/SC/0146; CONNECT 12/NW/0094) have received favourable ethical opinions to interview patients who have declined or withdrawn from trials.

Sampling and recruitment

Sampling of patients for the Information Study interviews will be purposive and aim to continue until data saturation is reached, which is anticipated will require 20 interviews(30). Sampling will be operationalized via a matrix to encompass diversity in key characteristics including trial participation status (patient consented, declined or withdrawn), treatment plan, surgery versus surveillance, patient demographics and trial site.

Recruitment of patients to the Information Study will be facilitated by clinicians and research nurses at the trial sites participating in the study. At the end of the appointments where SAVER has been introduced to patients, the clinician or research nurse will briefly outline the Information Study to patients. Clinicians/research nurses will hand interested patients the Information study PIS and seek their verbal permission for the qualitative researcher to contact the patient to discuss the study in further detail, and for the patient's contact details to be passed to the researcher (the qualitative researcher will seek the patient's informed consent

for the interviews at a later date). The Information Study is focused on the patients' views and experiences of SAVER i.e. regardless of whether or not a patient consents to the trial. Therefore, clinicians/research nurses at the relevant sites will be asked to discuss the interviews with all patients who have been approached about SAVER, during the period that the Information Study is open to recruitment at that site. Patient's contact details (name, address, telephone numbers, email address, age and gender) along with details of the recruitment consultation (clinician's contact details, date of consultation and whether or not consent was obtained for SAVER) will be recorded on a pro forma for the Information Study. These pro formas will be securely transferred to the researcher at the University of Liverpool via post, fax or uploaded directly to a network drive at the University of Liverpool via a secure upload facility. It will be made clear to patients that participation in the Information Study is voluntary and that not all patients will subsequently be contacted for an interview. All patients who express an interest in the Information Study but are not selected for interview will be contacted by letter to thank them for their interest.

8.5.2.4. Interviews

The qualitative researcher with proven skills in qualitative interviewing will contact selected patients to discuss the Information Study further, usually with 1-4 weeks of the appointment when SAVER was discussed. S/he will check patients have received the Information study PIS, explain about the study, answer any queries, and if patients are willing to proceed, arrange a convenient time for the interview. It is anticipated that most patients will be interviewed face-to-face in their own homes, although they will be able to opt for a telephone or Skype interview or to be interviewed in another place of their choosing if they prefer.Consent will be sought before interviews; for face-to-face interviews this will be written consent; for any telephone interviews consent will be audio-recorded as we have done in a previous HRA approved study (CONTRACT – 16/SC/0596. Telephone consent will involve the researcher reading each aspect of the SAVER Information Study consent form to participants. The researcher will initial next to each box on the consent form when the participant provides verbal consent, will add the participant name, date and "telephone/Skype interview" where the signature is required and will post or email a copy of the form to the participant. Informed consent discussions will be audio recorded for auditing purposes. All interviews will be audio-recorded and conducted and managed with sensitivity. Topic guided semi-structured interviews will explore patients' accounts of: the trial recruitment process; verbal and written information, influences on decision making, trial treatments, and procedures, and ways to improve on the trial design and process. Interviews will be conversational and participants will be free to decline to answer any questions or to stop the interviews at any point.

8.5.2.5. Analysis

Audio-recordings of interviews will be transferred to a professional transcription agency (with whom we have a legally binding confidentiality agreement) via a secure upload facility. Completed transcripts will be checked by the qualitative researcher on receipt and anonymised ready for analysis. Audio recordings of the interviews will be retained in case of further queries until the end of the study at which point the recordings will be destroyed. Analysis of interview transcripts will iterate with data collection to refine sampling and facilitate exploration of emergent topics. Analysis will be interpretive and draw on the framework method. Procedurally, this approach involves initial steps common to other methods of qualitative analysis: 'familiarization' with the data; using as mix of deductive and inductive coding to 'identify' or generate a framework of categories and sub-categories; and 'indexing' the data according to these categories. Coding will occur at multiple levels from detailed line-by-line coding to a more holistic approach, thereby helping to contextualize the analysis. The remaining elements of the framework approach are more unique: 'charting', whereby we will arrange summaries of the data into matrices according to the framework categories. This facilitates the final step, 'mapping', which involves exploring patterns within the data in ways

that connect to our aims to understand how SAVER and any future main trial can be improved from the perspective of patients. Bridget Young will provide overall leadership of the analysis and supervision of the qualitative researcher but key members of the wider team will be involved through meeting to discuss initial interpretations of the data and 'test' the developing analysis. NVIVO software will be used to assist the coding and indexing of the data. Beyond the above procedures the qualitative study will be informed by guidance on quality in qualitative research(31, 32). Nevertheless, we are aware that such procedures do not guarantee quality. Our overarching criterion for judging the quality of the analysis will consider its catalytic validity(31, 32), that is, its contribution to ensuring a deliverable trial which is understandable and acceptable to patients.

8.5.2.6 Information study recruitment logs

Recruitment logs at SAVER Information Study sites will record:

a. All patients who are eligible to be approached about SAVER and actually approached about SAVER or reasons not approached
b. whether or not verbal permission has been sought for the qualitative researcher to contact the patient and whether the patient gave permission or not

In addition, the qualitative researcher will maintain a log of all patients eligible to be interviewed, and those who were invited to be interviewed (and why), whether they accepted or declined and the number who went on to be interviewed. The qualitative researcher will liaise with trial teams to ascertain for each patient eligible for interview:

a. whether the patient consented to be randomized with SAVER or declined randomisation
b. whether a patient withdrew from SAVER post randomisation or at any stage prior to initiation of allocated treatment.

8.6 Loss to Follow-up

If any of the trial patients are lost to follow up, contact will initially be attempted through the PI at each centre. If the PI at the trial centre is not the patient's usual clinician responsible for their speciality care then follow-up will also be attempted through this clinician. Where all of these attempts are unsuccessful, the patient's GP will be asked to provide follow-up information to the recruiting centre.

8.7 Trial Closure

Investigators will be informed when patient recruitment is to cease.
Trial enrolment may be stopped at a site when the total requested number of subjects for the trial has been obtained.

The Independent Safety and Data Monitoring Committee (ISDMC) may recommend to the Trial Steering Committee (TSC) that the trial be stopped prematurely. Such premature termination/suspension of the trial will be notified to the MHRA and MREC as required.

The trial will be considered formally "closed" when the database is locked.

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

This section provides an overview of all statistical aspects of the study relating to SAVER: A randomised (1 Placebo:2 SV), double-blind, multi-centre placebo controlled phase II clinical trial investigating the use of sodium valproate in patients with a High Risk Oral Epithelial Dysplasia.

9.2 Method of Randomisation

Patients shall be allocated based on a 1:2 allocation ratio with the greater number of patients being allocated to the experimental arm. The sequences of allocation will be centrally generated by the LCTU study statistician using the Stata package *ralloc* employing permutated block randomisation with variable block size of 3 and 6. The allocation will be stratified by site and therefore separate randomisation lists will be created for each site.

9.3 Outcome Measures

9.3.1 Primary

Clinical activity will be measured using the commonly used surrogate end point that has evolved over several MD Anderson studies in the same field. The primary endpoint itself will be measured using the definitions of Mallery [20] and it will be derived as a composite score of changes in lesion size, changes in histological grade, and LOH definition.

Assessment of lesion size

Lesion size will be calculated based on a first assessment of clinical images with lesional size mm^2 = pixels of lesional area x 100/(pixels of 1 centimeter unit on the calibration device in the same image)^2. Secondary assessment of lesion size will be calculated based on the estimated elliptical area given by the longest length of the lesion and the associated perpendicular width.

Lesion size response will be then measured calculated on a 7 point scale ranging from -3 to 3 based on the change in lesion size between pre and post treatment assessment. Specifically, the relationship between score and outcome is as follows:

- 75% or more decrease = 3
- 50% to 74% decrease = 2
- 25% to 49% decrease = 1
- 0% to 24% decrease or increase = 0
- 25% to 49% increase = -1
- 50% to 74% increase = -2
- 75% or more increase = -3

Assessment of histology response score

Formally, a 0 to 8 grade scale will beused to obtain the histological score as follows:

- 0 = normal with or without hyperkeratosis
- 1 = atypia with crisply defined clinical margins
- 2 = mild dysplasia
- 3 = mild-moderate dysplasia

- 4 = moderate dysplasia
- 5 = moderate-severe dysplasia
- 6 = severe dysplasia
- 7 = carcinoma in situ
- 8 = invasive SCC

Assessment of LOH response score
A series of microsatellite markers will be selected for LOH analyses. These are 8 corresponding loci and associated genes:

- 3p14 [D3S1007 (VHL), D3S1234 (FHIT)]
- 9p21 [D9S171, D9S1748 (P16/CDKN2A), D9S1751 (P16)]
- 9p22 (IFN- a)
- 17p13 [D17S786 (P53) and TP53]

For each loci, a score of +1 is given if it is positive for LOH and 0 if it is negative for LOH.

Total responsiveness score
The total responsiveness score for each patient will be calculated as:

> **Response score = lesion size score + change in histological response score (pre-treatment grade – post-treatment grade) + change in LOH response score (pre-treatment score – post-treatment grade)**

Based on the responsiveness score, patients will be classified as follows:

- Response score ≤ -1– Disease Progression
- Response score between 1 and 1 – Stable Disease
- Response score ≥ 1 - Response

The only exception to the criteria laid out is for patients who have a confirmed malignant transformation. These patients shall automatically be confirmed as having disease progression, irrespective of their responsivness score.

The primary outcome for analysis is defined as the disease response rate which compares patients with response to treatment against patients with either stable disease or disease progression.

9.3.2 Secondary

Secondary endpoints include

- Disease control rate, defined as treatment response or stable disease against patients with disease progression using the composite responsiveness score defined in Section 9.3.1.
- Clinical response, as measured by assessment of lesion size as in Section 9.3.1.
- Histological response, as measured by assessment of histology response score as in Section 9.3.1.
- LOH Response score, as measured in 9.3.1.
- WHO grade of OED (or SCC) in entire whole resection specimen (where any oral resection is performed within trial period).
- Toxicity, measured using CTCAE (Version 4) classifications.

- Overall Survival measured as the time from randomisation until death by any cause.
- Time-to-malignancy of head and neck site, or any other diagnosed malignancy outside of head and neck, within that patient's 'active' trial period i.e. 6 months.
- Time-to-malignancy of head and neck site, from the time of randomization to the total time that trial is open, as derived from case note review carried out within the last 6 months of trial activity.
- Feasibility endpoints as in the section 'internal feasibility study' below.
- Qualitative and mechanistic studies as listed in relevant sections below.

9.4 Sample Size

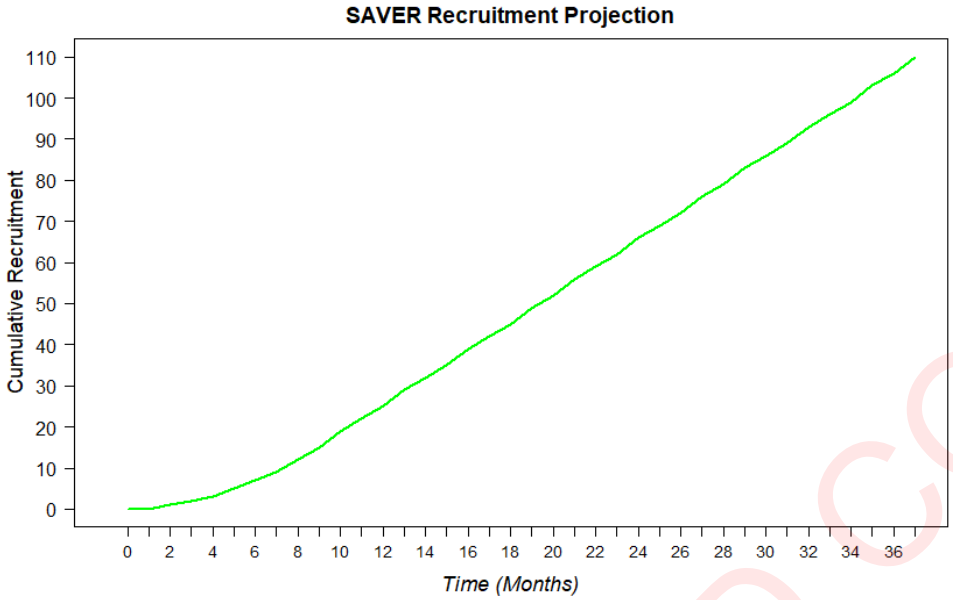
Sample size calculations are carried out on the principles of a Single Stage Jung design for randomised Phase II studies based on exact binomial probabilities and allowing for unequal allocation. The primary outcome is the response rate defined in Section 9.3.1 and is assumed to follow a binomial distribution. The estimated response rate in the control arm is $p_0 = 0.2$. A clinically important difference is represented by a difference relating to $p_1 > 0.4$ (i.e. an absolute difference of 0.2 between the two proportions). Based on Jung's design, 100 patients (33 receiving Placebo and 67 the experimental treatment) will be required in the study, with a Type I error rate of 0.16 and 82% of power. Table A gives an overview of Type I error rates and Power corresponding to different response rates in the two arms (always differing by 0.2). The table shows that even if the response rate in the control arm differs from from $p_0 = 0.2$, the Type I error will always remain below 0.17 and the Power will not drop below 0.82. Adjusting for a potential 10% drop-out rate, the final sample size will be of 110 patients (37 in the Placebo arm and 73 in the experimental arm).

Resp. rate (Arm 1: N=33)	**0.2**	**0.25**	**0.3**	**0.35**	**0.4**	**0.45**	**0.5**	**0.55**	**0.6**	**0.65**	**0.7**
Resp. rate (Arm 2: N=67)	**0.4**	**0.45**	**0.5**	**0.55**	**0.6**	**0.65**	**0.7**	**0.75**	**0.8**	**0.85**	**0.9**
Type I	0.13	0.15	0.17	0.16	0.16	0.16	0.16	0.16	0.16	0.15	0.15
Power	0.87	0.84	0.83	0.82	0.82	0.82	0.82	0.83	0.84	0.85	0.87

Table A: Type I error and Power for trial of 100 patients based and an absolute difference of 10% required to continue onto a phase III study.

9.5 Study recruitment

The intent of the study is to recruit the 110 patients required over a period of 37 months. Recruitment estimates are based on 10 sites recruiting at an average rate of 0.3 patients per site per month. It is further expected that sites open to recruitment at a rate of one per month. The figure below gives the expected recruitment rate.



9.6 Interim Monitoring and Analyses

There are no formal stopping rules for efficacy and no formal interim analysis based on patient response rate. An Independent Safety and Data Monitoring Committee (ISDMC) will however meet at least annually to assess the trial data and will be able to make recommendations as to the early termination of the study on grounds of toxicity or futility.

9.7 Internal feasibility study

The study is designed with an internal feasibility component to assess at regular intervals its capability of completion in a timely fashion.

The main feasibility outcome of interest is the recruitment rate. Targets for recruitment are set at 16, 49 and 83 patients for 12, 24 and 36 months of recruitment respectively. Note this does not include the time taken for study set-up.

It will be the job of the ISDMC to assess the feasibility of the study and to make appropriate recommendations to the TSC. As a guide, it is proposed that if the study is recruiting within 80% of the intended rate (with targets of 13, 39 and 66 patients for 12, 24 and 36 months respectively) then no action will be taken. If the study is recruiting between 50% and 80% of the intended rate (8-12, 25-38 and 43-65 patients for 12, 24 and 36 months respectively), the ISDMC may recommend continuation only if strategies will be put in place to increase recruitment (e.g. amendments to protocol or addition of extra sites). If the study is recruiting at less than 50% of the intended rate then the ISDMC may recommend early termination of the study on the grounds of feasibility.

Please note that these guidelines are a guide only and the ISDMC may wish to judge feasibility in light of other external factors relating to the study (e.g. difficulties in opening sites to recruitment/development of competing studies).

Further feasibility endpoints to be assessed during the initial months of the study will be:

- Randomisation to screening ratio: total number randomised/total number screened
- Patient drop-out rate
- Number of major protocol deviations

- Completeness of sample collection
- Assessment of drug compliance by plasma concentration of SV

These endpoints may alter the study protocol and associated study processes (e.g. CRF design) but are not expected to be a cause for early termination or any change to the overall study design.

9.8 Statistical Methodology

Full details of the planned analyses, including template tables and graphs, will be included in a separate Statistical Analysis Plan.

9.8.1 Timing of analysis

Final analysis of the study will take place once all patients have received a minimum of 4 months follow up required for the assessment of the primary endpoint.

9.8.2 Patient Groups

Final analysis will be carried out on an intention to treat (ITT) basis, retaining all patients in their initially allocated arms, irrespective of any protocol violations. However, toxicity analysis will be carried out on the basis of which treatment patients actually received.

9.8.3 Statistical Thresholds

Sample size calculation is carried out using a one-sided type I error rate of 0.16 and the final analysis will be assessed using a one-sided P-value of 0.16 as the threshold for statistical significance. The primary efficacy parameter (odds ratio) will also be presented alongside a one-sided 84% confidence interval.

All other analyses, including analyses of the secondary endpoints, will be assessed using a nominal two-sided P-value of 0.05 to determine statistical significance.

9.8.4 Missing Data

Missing data are not anticipated to be an issue in the study and final analyses will be carried out on a complete case basis. If substantial (>10%) missing data are observed on the primary endpoint or key prognostic covariates, multiple imputation techniques using chained equations shall be used.

9.8.5 Analysis of Primary Endpoint

The primary endpoint will be the response rate as defined in Section 9.3.1. The primary efficacy parameter is the odds ratio comparing sodium valproate to Placebo. Primary analysis shall be performed using a stratified Mantel Haenszel test. Further analyses shall be carried out using multivariable logistic regression, noting that this model shall be restricted to include only as many prognostic variables as the data allow based on the statistical rule of thumb of 10 response per degree of freedom.

9.8.6 Analysis of Secondary Endpoints

Analyses of the categorical secondary endpoints, disease control rate and toxicity shall mirror that of the primary analyses, using stratified Mantel Haenszel test and multivariable logistic regression techniques.

Analyses of time to event endpoints, overall survival and time-to-malignancy shall be carried out using stratified log rank test for comparisons across treatment groups. The efficacy parameter to assess these endpoints will be the hazard ratio. Further multivariable analyses shall be carried out using Cox proportional hazards models with the assumption of proportional hazards assessed via inspection of Schoenfeld residuals.

10 PHARMACOVIGILANCE

10.1 Terms and Definitions

The following definitions have been adapted from European Directive 2001/20/EC and ICH GCP E6

Adverse Event (AE)
Any untoward medical occurrence [i.e. any unfavourable or unintended sign (including abnormal laboratory results), symptom or disease} in a research participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

AEs include the following:

- All suspected adverse medication reactions.
- All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity.
- Apparently unrelated illnesses, including the worsening of a pre-existing illness.
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as two separate AEs.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. ***Laboratory abnormalities associated with a clinical event (e.g. elevated liver enzymes in a patient with jaundice) should be described in the comments of the report of the clinical event rather than listed as a separate AE.***

Adverse Reaction (AR)
Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR)
An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:
a) In the case of a product with a marketing authorization, in the summary of product characteristics for that product
b) In the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)
Any adverse event or adverse reaction is classified as serious if it:

a) results in death
b) is life-threatening* (subject at immediate risk of death)
c) requires in-patient hospitalisation or prolongation of existing hospitalisation**
d) results in persistent or significant disability or incapacity, or

e) consists of a congenital anomaly or birth defect
f) Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

Suspected Unexpected SAR (SUSAR)

Any suspected adverse reactions related to an IMP that is both unexpected and serious.

10.2 Notes on Adverse Event Inclusions and Exclusions

10.2.1 Include

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment
- Laboratory anomalies that require clinical intervention or further investigation (unless they are associated with an already reported clinical event)
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents

10.2.2 Do Not Include

- Medical or surgical procedures- the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Overdose of medication without signs or symptoms
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

10.2.3 Reporting of Pregnancy

Patients who become pregnant while receiving trial treatment must immediately discontinue said treatment.

If a patient becomes pregnant during trial treatment or gives birth within 43 weeks following the date of the last study treatment, a completed Pregnancy Report Form must be faxed to the LCTU within 24 hours of learning of its occurrence. On pregnancy

outcome, the final Pregnancy Report Form should be faxed to the LCTU within 28 days after the outcome. The final Pregnancy Report Form is used to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or new-born complications. Pregnancy follow-up information on this form also includes an assessment of the possible relationship to the trial medication of any pregnancy outcome.

Any SAE experienced during pregnancy must be reported on the SAE form.

Pregnancies of partners of male patients do not need to be reported.

The LCTU will report all pregnancies to the trial sponsor(s), MHRA and MREC.

10.3 Notes Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.
Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities
Life threatening
Death

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

10.4 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in table B.
If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. In the case of discrepant views on causality between the investigator and others, the MHRA will be informed of both points of view.

Table B: Definitions of Causality

Relationship	Description
None	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of

	other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Highly Probable	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

10.5 Expectedness

An AE whose causal relationship to the study drug is assessed by the investigator as "possible", "probable", or "highly probable" is an Adverse Drug Reaction.
All events judged by the investigator to be possibly, probably, or highly probably related to the IMP, graded as serious and **unexpected** for list of Expected Adverse Events (see Reference Safely Information section 10.6) should be reported as a SUSAR.

10.6 Reference Safety Information

The Reference Safety Information (RSI) to be used for this trial is as follows:

Epilim 500 Gastro-resistant tablets - Summary of Product Characteristics (SmPC) - Section 4.8

10.7 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.
When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

10.8 Reporting Procedures

All adverse events that occur from the point of randomisation are to be reported, even if the patient has not started taking the sodium valproate.

All adverse events should be reported up to the point of the primary endpoint being established, with the exception of any malignant transformation or new head and neck cancer, which should be collected until trial closure.

Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the LCTU in the first instance.

10.8.1 Non serious ARs/AEs

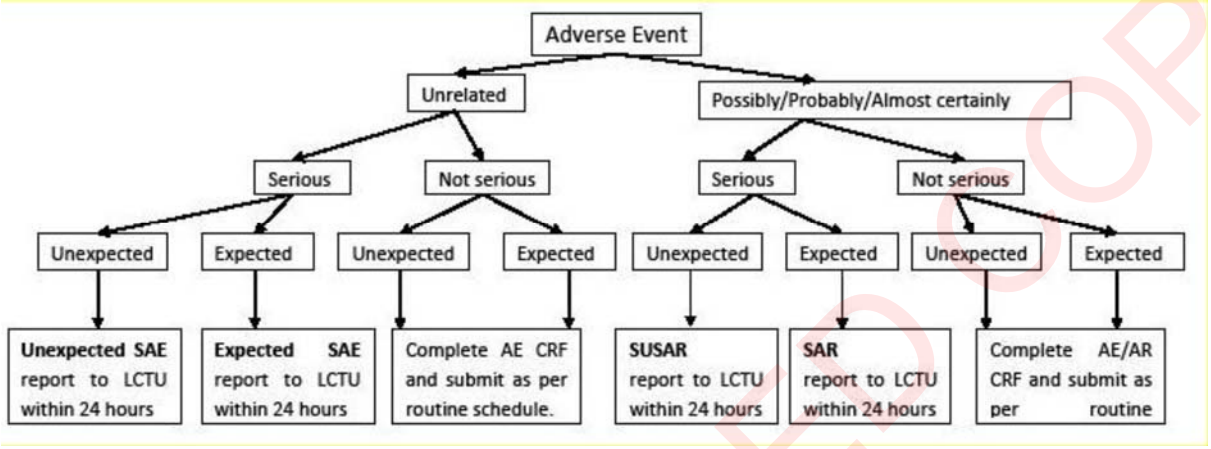
All such events, whether expected or not, should be recorded in the relevant page of the CRF.

10.8.2 Serious ARs/AEs/SUSARs

SARs, SAEs and SUSARs should be reported within 24 hours of the local site becoming aware of the event. The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should sign the causality

of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

The LCTU will notify the MHRA and main REC of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and /or SAEs as required by their Local Research Ethics Committee and/or Research & and Development Office.



10.9 Responsibilities – Investigator

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product.

All SAEs must be reported immediately by the investigator to the LCTU on an SAE form unless the SAE is specified in the protocol, IB or SmPC as not requiring immediate reporting. All other adverse events should be reported on the regular progress/follow-up reports.

Minimum information required for reporting:

- Study identifier
- Study centre
- Patient number (Trial Number)
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

i. The SAE form should be completed by the responsible investigator i.e. the consultant named on the 'signature list and delegation of responsibilities log' who is responsible for the patient's care. The investigator should assess the SAE for the likelihood that it is a response to an investigational medicine. In the absence of the responsible investigator the form should be completed and signed by a designated member of the site trial team and faxed to the LCTU immediately. The responsible investigator should check the SAE form, make changes as appropriate, sign and then re-fax to the LCTU as soon as possible. The initial report shall be followed by detailed, written reports.

ii. Send the SAE form by fax (within 24 hours or next working day) to the LCTU

Completed SAE Reports must be faxed within 24 hours of becoming aware of the event to the Liverpool Cancer Trials Unit

Fax Number: 0151 794 8931

iii. The responsible investigator **must** notify their R&D department of the event (as per standard local procedure).
iv. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.
v. Follow-up information is noted on another SAE form by ticking the box marked 'follow-up' and faxing to the LCTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.
vi. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

10.9.1 Maintenance of Blinding

Systems for SUSAR and SAR reporting should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. Unblinding clinicians may be unavoidable if the information is necessary for the medical management of particular patients. The safety of patients in the trial always takes priority. In each report, seriousness, causality and expectedness should be evaluated for all of the trial treatments unless criteria have been fulfilled and unblinding has taken place.
Cases that are considered serious, unexpected and possibly, probably or almost certainly related to one of the trial therapies (i.e. possible SUSARs) would have to be unblinded at the clinical trials unit prior to reporting to the regulator and re-evaluated for expectedness in light of the administered treatment.

10.10 Responsibilities – CR:UK LCTU

The LCTU is undertaking duties delegated by the trial sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA, competent authorities of other European member states in which the trial is taking place and, if required, the research ethics committees) as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the LCTU is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the LCTU first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:

a. A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial;
b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
c. A major safety finding from a newly completed animal study (such as carcinogenicity).
d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;

- Recommendations of the Independent Safety and Data Monitoring Committee, if any, where relevant for the safety of the subjects.

Staff at the LCTU will liaise with the designated Clinical Co-ordinator who will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported to regulatory authorities and MREC. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

The LCTU will also send an annual safety report containing a list of all SARs to regulatory authorities and

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

All issues raised here are included in the Patient Information Sheets (see Appendices).

Patients will be informed as to the balance of risks and benefits of entering the SAVER trial, the factors below carefully balanced in the patient information sheet, and as approved by the Research Ethics Committee (REC). Specifically these issues relate to:

- **Toxicity of Sodium Valproate.** SV at 1000mg/day is a low to medium dose, associated with mild or absent toxicities, and is well tolerated(18). Higher doses, sometimes justified in epilepsy, are associated with weight gain, tremor, drowsiness and cognitive slowing. In the context of premalignant H&N conditions, we feel that these would not be justified. The impact of weight gain will be reduced by excluding obese patients and teratogenic effects will be avoided by excluding women of childbearing age.
- **Potential risks of delay to therapy (in those patients listed for surgical excision).** An interim study visit at 2 months will mitigate any risk that lesions might undergo malignant transformation in the 4 month experimental window. This will allow clinical assessment of oral lesions and further to facilitate collection of toxicity / AE (Adverse Events) data. In total, SAVER patients will be clinically examined 5 times in the 6 month study, each time signs of malignant transformation will be sought and acted upon.
- **Benefits - Potential benefit to individual** – Surgery is not always possible for all lesions or all patients, and recurrence rates for premalignant lesions are high. Localised therapies fail to treat the wider field, often encompassing the entire upper aerodigestive tract, and therefore do not address the risk of multifocal lesions. The limitations of current treatments underscore the need for systemic agents in this setting(2).
- **Societal benefit**. There is no robust evidence that current standard therapy for OED is effective in reducing the risk of OSCC development. By researching potentially effective treatment of OED it may be possible to reduce the incidence of oral cancer,
- Vulnerable patients will not be recruited to the SAVER trial
- Additional visits required by the trial are minimal, typically one or two extra visit for screening / randomisation and one extra trial review at 2/12 (although this depends on existing local practices)
- Additional tests include blood tests, and possibly one additional biopsy.
- Use of placebo

11.2 Ethical Approval

The trial protocol has received the favourable opinion of a Multi-centre Research Ethics Committee (MREC) but all participating sites must undergo capacity and capability assessment. A copy of all site approval documents and a copy of the PIS and ICF on local headed paper should be forwarded to LCTU before patients are entered. The LCTU should receive notification of positive capacity and capability for each new centre via the site's R&D department.

11.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all patients participating in LCTU coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients by staff with appropriate experience. An appropriate Patient Information and Consent forms, describing in detail the trial interventions/products, trial procedures and risks will be approved by an independent ethical committee (IEC) and the patient will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the patient and answer any questions that may arise. A contact point where further information about the trial may be obtained will be provided. This is usually the contact details of the Research Nurse and/or the Principal Investigator at site where the patients can obtain further information about the trial.

After being given adequate time to consider the information, the patient will be asked to sign the informed consent document. A copy of the informed consent document will be given to the patient representative for their records and a copy placed in the medical records, with the original retained in the Investigator Site File.

The patient may withdraw from the trial at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

11.4 Study Discontinuation

In the event that the study is discontinued, there are no provisions for patients to be unblinded or to continue on study medication.

12 REGULATORY APPROVAL

This trial has been registered with the MHRA and has been granted a Clinical Trial Authorisation (CTA). The CTA reference is <<insert CTA number>>

13 TRIAL MONITORING

Central and site monitoring is conducted to ensure protection of patients participating in the trial, and that trial procedures, trial intervention administration, laboratory and data collection processes are of high quality and meet sponsor and, when appropriate, regulatory requirements. A risk assessment will be carried out to determine the level of monitoring required, and a subsequent monitoring plan will be developed to document who will conduct the central and site monitoring, at what frequency monitoring will be carried out and the level of detail at which monitoring will be conducted.

13.1 Risk Assessment

In accordance with the LCTU Standard Operating Procedure a risk assessment will be completed in partnership with the following:

- Trial Sponsor
- Chief Investigator
- Trial Coordinator
- Trial Statistician

In conducting the risk assessment, the contributors will consider potential patient, organisational and trial hazards, the likelihood of their occurrence and resulting impact should they occur.

The outcome of the risk assessment will be assigned according to the following categories:

- Type A: no higher than that of standard medical care
- Type B: somewhat higher than that of standard medical care
- Type C: markedly higher than that of standard medical care

Sodium Valproate is used for the first time in patients with high-risk Oral Epithelial Dysplasia (OED). As a result, this trial has been categorised as a CTIMP Type B and is therefore somewhat higher than the risk of standard medical care.

13.2 Source Data and Documents

- Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original copies or certified copies). (ICH E6, 1.51.)
- Examples of these documents, data and records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratory departments involved in the clinical trial. (ICH E6, 1.52.)

In order to resolve possible discrepancies between information appearing in the CRF and any other patient related documents, it is important to know what constitutes the source document

and therefore the source data for all information in the CRF. Data recorded in the CRF should be consistent and verifiable with source data in source documents *other* than the CRF (e.g. medical record, laboratory reports and nurses‟ notes).

Each participating site should maintain appropriate medical and research records for this trial, in compliance with ICH E6 GCP, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects.

For data where no prior record exists and which are recorded directly in the CRF (e.g. inclusion/exclusion criteria, adverse events and Quality of life questionnaires), the CRF will be considered the **source document,** unless otherwise indicated by the investigator.

In addition to the above, date(s) of conducting informed consent including date of provision of patient information, trial number and the fact that the patient is participating in a clinical trial should be added to the patients' medical record contemporaneously.

13.3 Data Capture Methods

Trial data will be captured using an electronic Case Report Form (eCRF), with the exception of randomisation which will be processed on paper CRF.

- Once the patient is randomised, all trial related data up to that point shall be input as soon as possible and definitely within 1 week
- Treatment visit data shall be input within 2 weeks of the patient visit.
- Should the patient end trial participation for any reason, this data shall be input as soon as possible and definitely within 1 week.

In case of the database being off-line for any prolonged period, a 'back-up' paper CRF will also be available via the LCTU portal.

13.3.1 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained.

eCRF data collection fields will only activate if data is required.

If a space on the paper CRF is left blank because the procedure was not carried out or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Paper CRF pages are available to download from the LCTU portal.

13.4 Monitoring at LCTU

There are a number of monitoring features in place at the LCTU to ensure reliability and validity of the trial data.

The Green Light Process in place at the LCTU means that no patients can be registered at a particular site without the green light having been given. It ensures that all approvals must be

in place, all contracts/agreements signed and all trial-specific and ICH GCP training received by site research staff before patients can enter the trial.

LCTU staff members receive appropriate randomisation training and there is always office cover to ensure the randomisation procedures are carried out correctly. The TC maintains a record of randomisation errors and notifies the trial statistician as they occur. Randomisation problems are monitored by the ISDMC, and if it is noted that a particular site is making consistent errors in the consent or randomisation processes, additional training will be provided by the TC to rectify the problem.

Central Monitoring reports will be generated regularly and circulated to the Trial Management Group and Sponsor. These reports will be analysed to identify pharmacovigilance reporting, protocol deviations, Corrective and Preventative Actions raised against the study, data query data, recurring problems/issues at sites or the trial as a whole including, but not limited to, patient screening failures, randomisation problems, recruitment totals etc.

Data stored at LCTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. If any such problems are identified, a photocopy of the problematic CRF(s) will be returned to the local site by post or fax for checking and confirmation or correction, as appropriate – any data which are changed should be crossed through with a single line and initialled (see section 13.3.1). The amended version should be returned to LCTU and the site's copy should also be amended. LCTU will send reminders for any overdue and missing data.

13.5 Clinical Site Monitoring

13.5.1 Direct access to data

In order to perform their role effectively, monitors and persons involved in Quality Assurance and Inspection will need direct access to primary subject data, e.g. patient records, laboratory reports, appointment books, etc. As this affects the patient's confidentiality, this fact is included on the Patient Information Sheet and Informed Consent Form.

13.5.2 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Case report forms will be labelled with patient initials and unique trial randomisation number. Tissue samples will be transferred to both the pathology and GCLP laboratories and will be identifiable by unique trial randomisation number only. Consent forms sent to the LCTU as part of the randomisation process may contain patient identifiers for the purpose of monitoring as described in the trial risk assessment. Such information will be stored separately from the patient folders in secure, locked cabinets.

13.5.3 Quality Assurance and Quality Control of Data

Quality Assurance (QA) includes all the planned and systematic actions established to ensure this trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. Quality Control (QC) includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled.

The SAVER investigational sites, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit and inspection by competent or independent ethics committees and the LCTU. Such audits/inspections may take place at any sites where trial related activity is taking place (i.e. the Sponsor site(s), Cancer Research UK (CR-UK)

Liverpool Cancer Trials Unit or at any investigators site, including laboratories, pharmacies etc.

The site staff shall assist in all aspects of audit/inspection and be fully cognisant of the LCTU communication strategy for multicentre trials. This includes management systems for the green light process or drug release to site, conforming to the total Quality Management System currently operating within the LCTU.

13.5.4 Records Retention

Essential documents should be retained until at least 2 years after last approval of a marketing application in an ICH region and until there are no ending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product. These documents should be retained for a longer period however if required by applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained. (ICH GCP 4.9.5)

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Trial File, until the LCTU informs the investigator that the documents are no longer to be retained.

In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The LCTU undertakes to store originally completed CRFs and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only.

At the point where it is decided that the trial documentation is no longer required; the Investigator will be responsible for the destruction of all site trial specific documentation and the Sponsor/LCTU will be responsible for the destruction of all trial related materials retained by the Sponsor/LCTU.

Verification of appropriate informed consent will be enabled by the provision of copies of participants' signed informed consent forms being supplied to the LCTU by recruiting centres. This requires that name data will be transferred to the LCTU, which is explained in the PIS. The LCTU will preserve the confidentiality of participants taking part in the study and the University of Liverpool is a Data Controller registered with the Information Commissioners Office.

14 INDEMNITY

SAVER is sponsored by the University of Liverpool and co-ordinated by the LCTU in the University of Liverpool. The University of Liverpool does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

The University of Liverpool does not accept liability for any breach in any hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

The University of Liverpool has vicarious liability for the actions of its staff, when through the course of their employment they are involved in the design and initiation of a clinical trial, including but not limited to the authorship of the Clinical Trial Protocol. The University of Liverpool has appropriate insurance in place to cover this liability.

15 FINANCIAL ARRANGEMENTS

Finite travel costs are available to patients to cover travel expenses incurred in attending hospital for the non-routine visits.

16 TRIAL OVERSIGHT COMMITTEES

16.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical), representative of the sponsor and members of the LCTU. The TMG will be responsible for the day-to-day running and management of the trial and will meet at least 3 times a year.

16.2 Trial Steering Committee (TSC)

The Trial Steering Committee will consist of an independent chairperson, other independent experts in the field of oral cancer, a statistician and at least one patient representative. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

Membership details of the TSC are available from the LCTU.

16.3 Independent Safety and Data Monitoring Committee (ISDMC)

The independent Safety and Data Monitoring Committee (ISDMC) consists of an independent chairperson in a related area of expertise, plus 2 independent members, one of whom is also an expert in a related area of expertise, and another whom is an expert in medical statistics.

The ISDMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The ISDMC will first convene before the trial opens to recruitment and will then define frequency of subsequent meetings (at least annually). Details of the interim monitoring and analyses are provided in section 9.6.

The ISDMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the study.

17 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and ISDMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

18 PROTOCOL AMENDMENTS

18.1 Version 2 (16/04/2018)

Original Approved version.

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20 APPENDIXES

Appendix 1. SOP for Women with childbearing potential

SAVER TRIAL

STANDARD OPERATING PROCEDURE

SOP details
SOP title: Women with childbearing potential: algorithm for determining eligibility for trial
Version number: 1
Version date: 26th October 2017

SOP Author Details
Author Name: Dr. Caroline McCarthy & Dr. Joseph Sacco
SOP Reviewer: Prof. Richard Shaw

Table of Contents

1. Background

"Women with childbearing potential (<2 years post menopause), pregnancy, breast feeding" is listed as an exclusion criterion within the SAVER protocol (section 5.2).

This is due to the teratogenicity of Sodium Valproate and the risk of valproic acid-induced hepatotoxicity in infants receiving breastmilk from a mother taking Sodium Valproate. Pregnant women and women who are breastfeeding will be excluded from the trial.

This document has been produced to guide clinicians recruiting women to the SAVER trial when their childbearing potential may be unclear. A woman with childbearing potential is defined as a premenopausal female capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception; women who are single; women whose husbands have been vasectomised or whose husbands have received or are utilising mechanical contraceptive devices.

Women who are non-smokers and have oral epithelial dysplasia on the lateral border of their tongue are known to be at high risk of developing oral cancer; these are an interesting group of women, whom it would be desirable to recruit to the SAVER trial. After the age of 45 years the chance of becoming pregnant dramatically reduces and we want to safely include this group of women in the trial. A flow-chart will be used to assess the womens' likelihood of becoming pregnant and their desire to comply with instruction regarding contraception will be assessed.

Although fertility significantly reduces from the age of 40 years, the chances of falling pregnant from age 45 years onwards is extremely low. Therefore, 45 years will be used as a cut-off point, below which women will not be considered for the trial.

Women over the age of 45 years who are not sexually active with men, or who are sexually active but are willing to confirm their intention to use effective contraception during the trial, will be eligible for recruitment. They will receive counselling on the risk to the foetus should they become pregnant whilst taking Sodium Valproate.

According to the European Medicines Agency (ICH M3), in general, women of childbearing potential should be using highly effective contraception to participate in clinical trials. A negative pregnancy test and study entry only after a confirmed menstrual period are recommended.

2. Purpose

To describe the process of determining a women's eligibility for inclusion in the SAVER trial, given than "women with childbearing potential" is a broad definition.

3. Scope

This document applies to all persons involved in recruiting patients to the SAVER trial.

4. *Roles and Responsibilities*

Anyone involved in patient recruitment to SAVER should be familiar with the protocol and the need to implement this SOP in relevant cases.

5. Procedure

The flow chart (figure 1) will be used to assess the women's likelihood of becoming pregnant during the trial and therefore whether or not she should be eligible for the trial.

Pre-menopausal female patients over the age of 45 will be asked if they are sexually active with men, or intend to be during the trial period. If they answer yes they will be asked if they are willing to use a highly effective form of contraception (see below). If they are prepared to do so, the patient will be counselled on the risks to the foetus, should she fall pregnant whist taking Sodium Valproate. If the patient is able to understand and retain that information and still wishes to go ahead with the trial, she will be considered in the same way as other potentially eligible patients, following a negative pregnancy test.

Adequate methods of effective contraceptive include (MHRA):

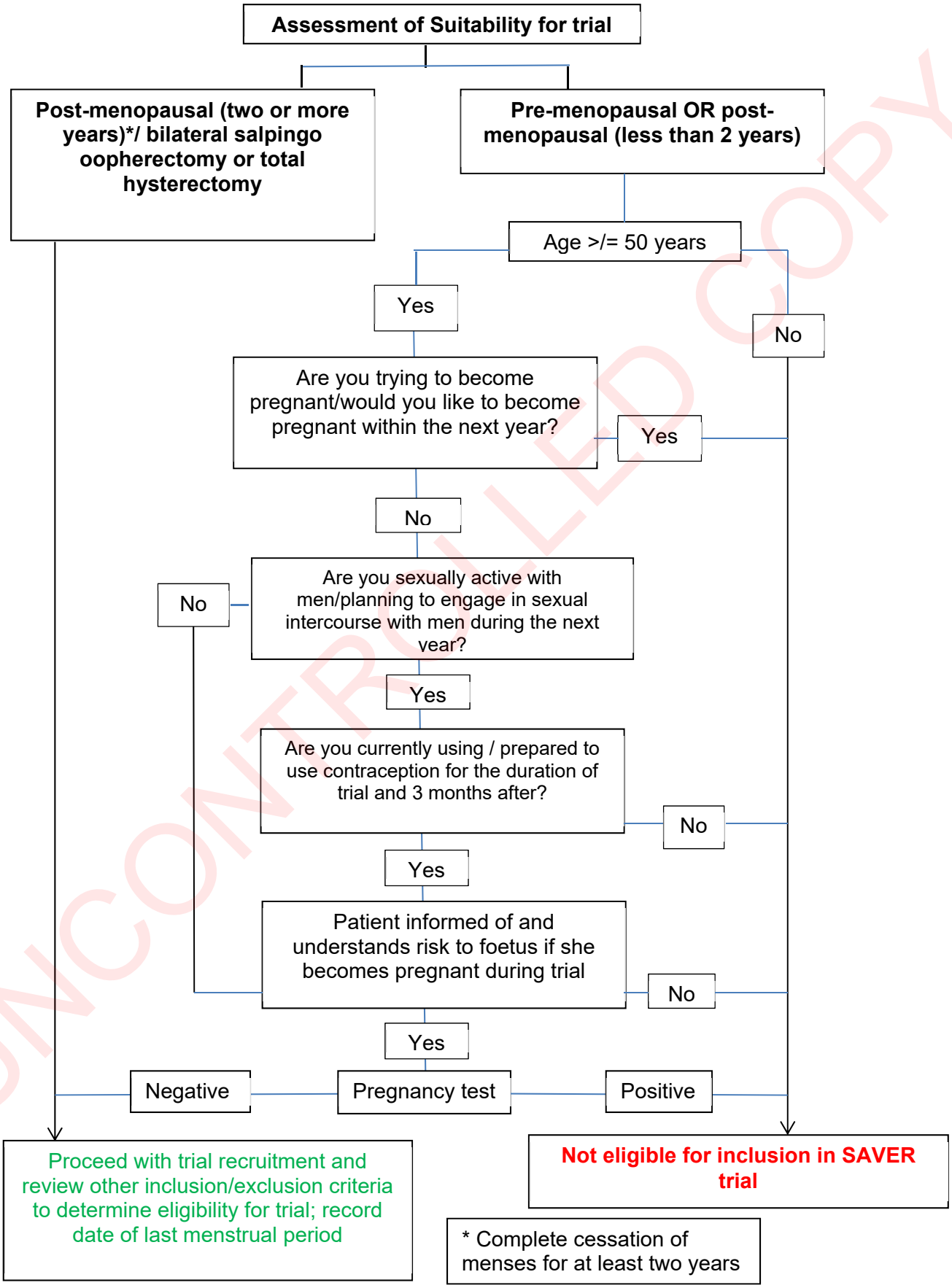
- Oral, injected or implanted hormonal methods of contraception
- Placement of an Intra-Uterine System or Intra-Uterine Device
- Barrier methods of contraception
- Male sterilisation
- True abstinence (only when this is the preferred and usual lifestyle of the participant).

Any subject, who, despite the requirement for adequate contraception, becomes pregnant during the trial will be withdrawn from the trial immediately and the reason for withdrawal (e.g. pregnancy) should be recorded in detail on the "Study Termination" CRF as well as on the subject's medical records. A "Pregnancy Report" CRF will be completed as soon as possible, and pregnancy outcome information will be obtained for "Pregnancy Follow-up" CRF.

6. Associated Documents

SAVER protocol.

Figure 1. Flowchart for assessment of eligibility of Women for the SAVER trial



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Appendix 2. Pathology SOP for SAVER trial:

Pathology for SAVER trial

1.0 Purpose and scope, applications

This is a standard operating procedure (SOP) for the clinical trial called SAVER (Chief Investigator: Professor Richard Shaw, University of Liverpool). The purpose is to describe the tissue pathway for biopsy specimens associated with the SAVER trial. The SOP applies to all specimens submitted to the 'Central Laboratory' (Cellular Pathology, Newcastle upon Tyne Hospitals NHS Foundation Trust) from SAVER trial participating sites.

2.0 COSHH / Health & Safety

INSERT references to SOPs for trimming, processing, embedding, sectioning and staining.

3.0 Personnel

Appropriately trained medical secretaries, biomedical scientists and pathologists.

4.0 Equipment / reagents

INSERT references to SOPs for trimming, processing, embedding, sectioning and staining.

4.1 References

SAVER study protocol

Mallery SR, Tong M, Shumway BS, Curran AE, Larsen PE, Ness GM, Kennedy KS, Blakey GH, Kushner GM, Vickers AM, Han B, Pei P, Stoner GD. Topical application of a mucoadhesive freeze-dried black raspberry gel induces clinical and histologic regression and reduces loss of heterozygosity events in premalignant oral intraepithelial lesions: results from a multicentered, placebo-controlled clinical trial. *Clinical Cancer Research*, 2014; **20**:1910-1924.

4.2 CPA

Standards A8.1 F2.1

4.3 Departmental policy

Not applicable.

4.4 Forms

Not applicable.

4.5 Related Documents

Not applicable

5.0 Procedure

Pathology for SAVER trial

Following consent to take part in the SAVER trial and registration with the Co-ordinating Centre, 5mm punch biopsies (baseline biopsy or primary end point biopsy) will be taken at the Participating Centre. The biopsy will be placed in 10% neutral buffered formalin (NBF) in a secure specimen container, the Trial Specific Pathology Form will be completed and the samples will be dispatched to the 'Central Laboratory' by registered first class post.

Central Laboratory address:

SAVER Clinical Trial (URGENT SPECIMEN)
Dr Max Robinson
Department of Cellular Pathology
Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
NE1 4LP

Contacts:
max.robinson@ncl.ac.uk
Tel: 0191 2824445
Fax: 0191 2825892

Trial samples received at the Central Laboratory will be allocated an iLAB accession number along with an associated barcode for tracking purposes (Trial specific study code=MRSAVER, SAVER trial number=Surname, patient initials=First name). The core biopsy will be bisected along the long axis and processed to paraffin wax. The formalin-fixed paraffin-embedded tissue block will be trimmed and three 4µm sections will be cut and stained with haematoxylin and eosin (H&E). Additional sections and stains may be required to derive a diagnosis (e.g. DPAS, p16 immunohistochemistry, high risk HPV in situ hybridisation). The sections will be graded independently by two pathologists using the SAVER trial designated grading system (Mallery et al., 2014). Discrepancies between epithelial dysplasia grades will be resolved by slide review and consensus. The data will be recorded in the iLAB pathology report, which will be scanned (pdf document) and emailed to the Participating Centre and the Co-ordinating Centre. The slides will be scanned on a digital pathology platform and the files stored on The Department of Cellular Pathology server. The slides and block will be archived in The Department of Cellular Pathology, Newcastle Royal Victoria Infirmary according to local standard operating procedures.

If the baseline biopsy shows no epithelial dysplasia or evidence of squamous cell carcinoma, the Participating Centre and the Co-ordinating Centre will be informed and the patient will be withdrawn from SAVER. The slides, block and pathology report will be returned to the Participating Site.

Biopsies taken during clinical care in the period that the SAVER trial is open, but outside the 'window' of drug delivery

If the clinical team intend to biopsy any other oral potentially malignant disorder during the period that the SAVER trial is open, the patient will be asked to consent for the specimen to be submitted to the 'Central Laboratory' for processing and diagnosis. The sample should be prepared according to the instructions for the 'baseline biopsy' and 'primary end point biopsy' (described above).

If the clinical team intend to excise the index lesion during the period that the SAVER trial is open, the patient will be asked to consent for the specimen to be submitted to the 'Central Laboratory' for processing and diagnosis. If feasible a 5mm punch biopsy should be taken prior to surgical excision and prepared according to the instructions for the 'baseline biopsy' and 'primary end point biopsy' (described above). The excision specimen can then be fixed in 10% NBF for routine pathological assessment.

Work flow

Day 1
Specimen reception staff receive the SAVER specimen and assign an accession number on the iLAB Pathology System (Trial specific study code=MRSAVER, SAVER trial number=Surname, patient initials=Forename).

Dr Max Robinson describes the formalin-fixed specimen, bisects the specimen and places it in a cassette for routine processing.

Day 2
Specimen embedded in paraffin wax.

Three 4µm sections stained with H&E.

Slides allocated to Dr Max Robinson for diagnosis.

Slides passed to second pathologist for diagnosis (Dr Chambers, Professor Sloan, Dr Okpokam).

Slide review and consensus diagnosis if required.

Pathology report composed and emailed to the Participating Centre and Co-ordinating Centre.

Slides and block archived in Department of Cellular Pathology, Newcastle Royal Victoria Infirmary.

Quality objective
The turnaround time from specimen receipt to sending the pathology report to the Participating Centre and Co-ordinating Centre will be 3 working days in 90% of cases.

Safety measures

The pathology reports will be monitored by the Chief Investigator and discussed at the Trial Management Group. Any concerns regarding 'Central Pathology Services' should be directed to Dr Max Robinson and if necessary will be investigated by the Department of Cellular Pathology Quality Manager. Any significant deviations from the SAVER trial protocol will raise a non-conformity which will be recorded in Q Pulse as a CAPA (Corrective Action Preventive Action) event.

Appendix 3. LIVERPOOL ADVERSE EVENTS PROFILE – SAVER TRIAL:

LIVERPOOL ADVERSE EVENTS PROFILE – SAVER TRIAL

During the last eight weeks have you had any of the problems listed below? Yes ☐ No ☐

For each item, if it has always or often been a problem ring ④. If it has sometimes been a problem ring ③ and so on.

Please be sure to answer every item.

		Always or often a problem	Sometimes a problem	Rarely a problem	Never a problem
a)	unsteadiness.....	4	3	2	1
b)	tiredness.....	4	3	2	1
c)	restlessness.....	4	3	2	1
d)	feelings of anger or aggression to others.	4	3	2	1
e)	nervousness and/or agitation.....	4	3	2	1
f)	headache.....	4	3	2	1
g)	hair loss.....	4	3	2	1
h)	problems with skin(e.g. acne, rash).....	4	3	2	1
i)	double or blurred vision.....	4	3	2	1
j)	upset stomach.....	4	3	2	1
k)	difficulty in concentrating.....	4	3	2	1
l)	trouble with mouth or gums.....	4	3	2	1
m)	shaky hands.....	4	3	2	1
n)	weight gain.....	4	3	2	1
o)	dizziness.....	4	3	2	1
p)	sleepiness.....	4	3	2	1
q)	depression.....	4	3	2	1
r)	memory problems.....	4	3	2	1
s)	disturbed sleep.....	4	3	2	1
t)	any other problem (please list in the space below and ring the appropriate number to indicate your response				
	aa)	4	3	2	1
	bb)	4	3	2	1