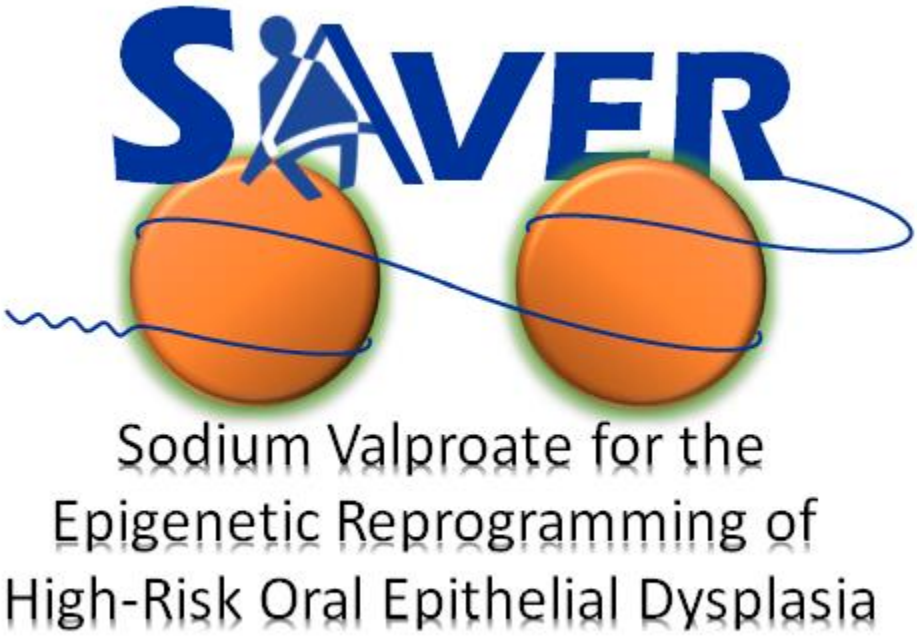

SAVER Protocol
V10.00, 31.05.2022

Study Sponsor(s):
The University of Liverpool
Clinical Directorate
Thompson Yates Building
The Quadrangle
Brownlow Hill
Liverpool L3 5RB

EudraCT number: 2018-000197-30

CTA Ref Number: 04196/0048/001-0005

ISRCTN12448611

Research Ethics Ref: 18/NW/0180

Sponsor Ref: UoL001289

Funder Ref: EME - Project: 14/209/13

NIHR Study ID 37192

Protocol Approval

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

Authorised by Chief Investigator:

Signature: See accompanying email approval confirmation **Date:** 01/08/2022

Full Name: **Professor Richard Shaw**
Professor of Head & Neck Surgery, Associate Director & Surgical Oncology Specialty Lead, NIHR Clinical Research Network (Cancer), Honorary Consultant in Oral & Maxillofacial / Head & Neck Surgery

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

Authorised on behalf of Sponsor:

Signature: See accompanying email approval confirmation **Date:** 01/08/2022

Karen Wilding
Senior Clinical Research Governance Manager
Clinical Directorate
University of Liverpool

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

Authorised on behalf of the Lead Statistician:

Signature: See accompanying email approval confirmation **Date:** 01/08/2022

Title, Name: **Liam Whittle**
Trial Statistician
Liverpool Clinical Trials Centre, University of Liverpool

General Information

This document describes the SAVER trial and provides information about procedures and recruitment 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. Any amendments will be circulated to the investigators participating in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Liverpool Clinical Trials Centre (LCTC) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the Chief Investigator, Professor Richard Shaw, via LCTC.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 12.

Liverpool Clinical Trials Centre Merger

During the management of the SAVER trial, the Liverpool Cancer Trials Unit (LCTU) and the Clinical Trial Research Centre (CTRC) have merged to become the Liverpool Clinical Trials Centre (LCTC). The LCTC will continue to use the LCTU PORTAL as a legacy system for the duration of this trial, for the purposes of this protocol it will be referred to as the LCTC PORTAL.

The Liverpool Clinical Trials Centre has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The Liverpool Clinical Trials Centre has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system.

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, LCTC 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.

Contact Details: Institutions

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Dr Richard Jackson Liverpool Clinical Trials Centre University of Liverpool Block C, Waterhouse Building 1-3 Brownlow Street L69 3GL Tel: 0151 795 5288 Fax: 00 44 (0) 151 794 8930 Email:r.j.jackson@liverpool.ac.uk	Julie Perry Liverpool Clinical Trials Centre University of Liverpool Block C, Waterhouse Building 1-3 Brownlow Street L69 3GL Tel: 0151 795 8577 Fax: 00 44 (0) 151 794 8930 Email: julie.perry@liverpool.ac.uk	N/A

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
FFPE	Formalin-fixed paraffin-embedded
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
LCTC	Liverpool ClinicalTrials Centre
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 (Gastro resistant)
TARDIS	Treatment Allocation RanDomIsation System
TC	Trial Coordinator
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
WOCBP	Women of childbearing potential

1 PROTOCOL OVERVIEW

Title: SAVER (Sodium Valproate for Epigenetic Reprogramming in the Management of High Risk Oral Epithelial Dysplasia) is a randomised, unblinded, 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):**

- 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
- 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 gastro resistant 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: No medication received

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

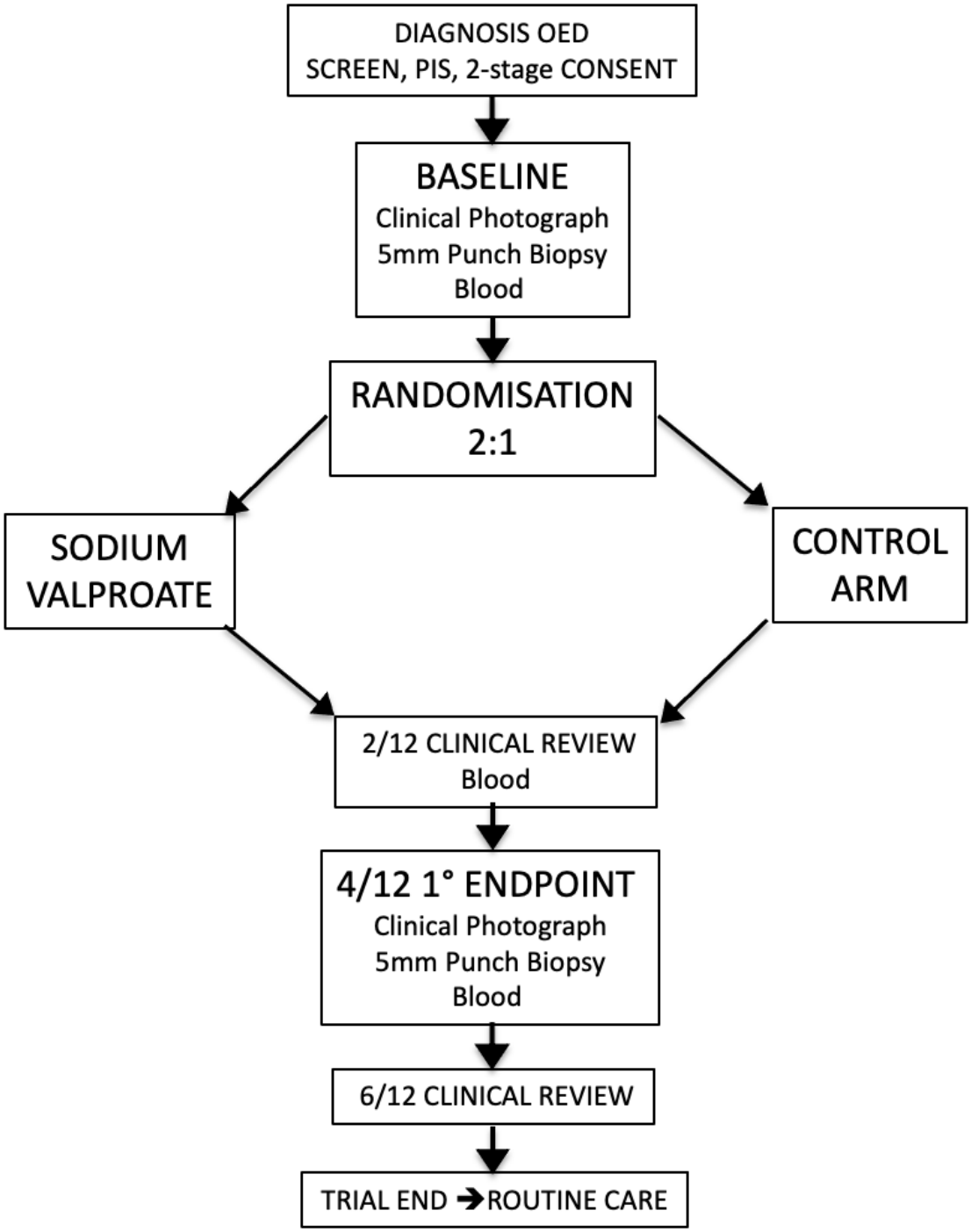
- changes in lesion size,
- histological grade, and
- allelic imbalance

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

1.1 Schematic of Study Design



2 INTRODUCTION

2.1 Background Information

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.

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 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 ROLES AND RESPONSIBILITIES

Sponsor

The Sponsor name is the University of Liverpool and is legally responsible for the study. They will formally delegate specific Sponsoring roles to the Chief Investigator and Clinical Trials Unit.

Funder

This study is funded by NIHR/EME Programme. This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results

Chief Investigator

Professor Richard Shaw is the Chief Investigator for the trial and is responsible for overall design and conduct of the trial in collaboration with other members of the study team.

Principal Investigators

In each participating centre a principal investigator will be identified to be responsible for identification, recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

Clinical Trials Unit

LCTC at the University of Liverpool in collaboration with the Chief Investigator, will have overall management responsibility and will be responsible for trial management activities including (but not limited to) study planning, budget administration, Trial Master File management, safety reporting, data management, randomisation, statistical analysis, participating site coordination and IMP management.

Oversight Committees

SAVER trial is subject to oversight and full details can be found in Section 16

4 STUDY DESIGN

4.1 Overall Design

SAVER is a phase II randomised controlled clinical trial with embedded mechanistic and feasibility studies, with a planned recruitment of 110 patients. The randomisation is in the ratio 2 SV (73 patients) :1 control (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 End of Study Definition

The end of the study is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database.

4.3 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. An acceptable variance from this time point is allowed for pragmatism, such that a window of:

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

(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.)

4.4 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

4.5 Study Setting – 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.

4.6 Selection of Participating Sites/Clinician Inclusion Criteria

Centres/Sites fulfilling the trial-specific criteria will be selected to be recruitment centres for the SAVER trial and will be opened to recruitment upon successful completion of all global (examples below) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to the LCTC. Initiation of sites will be undertaken in compliance with LCTC internal processes. Conditions and documentation required will be detailed on a LCTC Green Light Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

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

4.7 Selection of Principal Investigators

Principal Investigators will be required demonstrate equipoise, relevant experience and commitment during early stage feasibility assessment. All investigators will have the particular medical expertise necessary to conduct the study in accordance to the protocol and all regulatory and ethical requirements. Written agreement to conduct research as such will be obtained prior to site initiation.
A suitable co-investigator should be identified at each site to deputise in case of PI absence.

4.8 Centre/Clinician Exclusion Criteria

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

5 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

1. A diagnosis of oral epithelial dysplasia confirmed via 5mm punch biopsy reported by SAVER trial pathologist. The index lesion must be considered to be 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).

2. An 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 patient is fully informed, has received PIS (Patient Information Sheet) & considered during a 'cooling-off' period, is competent to consent, and is able to comply with minimum attendance requirements.

5. Age ≥ 18 years.

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. OSCC susceptible conditions e.g. Fanconi Anaemia, Blooms syndrome, Ataxia Telangectasia, Li Fraumeni syndrome etc.
4. Clinical and/or histopathological diagnosis of oral submucous fibrosis
5. Immunosupression, however, low dose i.e. <10mg/day prednisolone, or equivalent steroid, (as per BNF conversion table), are not considered an exclusion.
6. A patient who has received sodium valproate medication within the last 10 years
7. Epilepsy that has led to the use of *any* antiepileptic therapy within the last 10 years
8. Obesity (Body Mass Index >= 35)
9. 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, as defined by Child-Pugh Group C (see appendix 5)
d. current hepatic dysfunction (as evidenced by LFTs significantly outwith reference range or prolonged prothrombin time)
e. Past history or current pancreatitis
f. Women with child-bearing potential. A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
   Women who have undergone total hysterectomy or bilateral salpingo-oophorectomy or who are in a postmenopausal state are eligible for the SAVER trial. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range will be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). Females on HRT must discontinue HRT to allow confirmation of postmenopausal status before study enrolment. Otherwise, they must be considered non-eligible to participate in this trial and excluded.
g. 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, high dose salicylates including aspirin >75mg daily (patients taking low dose aspirin 75mg daily are eligible)
h. 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.
i. Patients with known or suspected mitochondrial disease, systemic lupus erythematosus or hyperammonaemia

5.3 Patient Transfer and Withdrawal

In consenting to the trial, patients agree to all trial activities including administration of trial intervention and treatment, follow-up assessments / visits and data collection. Every effort should be made to facilitate the completion of these for every recruited participant. If it is not possible to complete these activities (or it is deemed inappropriate) the reasons why should be documented.

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 LCTC 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:

- **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.

- **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).

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

- **Pregnancy**

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 Participant Withdrawal from Follow Up

Participants are free to withdraw from follow-up at any time without providing a reason, though a reason should be recorded if one is given. Those who wish to withdraw from further follow-up will have the data collected up to the point of that withdrawal included in the analyses. The participant will not contribute further data to the study and the CTU should be informed via email to the CTU and via completion of a Withdrawal CRF to be returned to the CTU within 7 days.

If participants express a wish to withdraw from follow up, the research team at site should ascertain if this is for all elements of trial follow-up, or if for example data from routine assessments can still be collected for the trial. In the case of ongoing adverse events,

participants should be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable. Any SAEs will be notifiable to the CTU via processes detailed in Section 10 even if a participant has withdrawn from follow up.

Also see section 8.6 Loss to Follow-up

5.3.4 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

** For recruitment and follow up of SAVER patients during the COVID-19 pandemic era, please refer to Appendix 2 - COVID-19 SAVER recruitment policy.

6.1 Participant Identification and Screening

Potentially suitable patients will be screened for eligibility for the SAVER trial using the screening log provided via the LCTC portal www.lctu.org.uk.

The patient will be provided with a '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.

Patients with a recent (non trial) diagnostic biopsy indicating their likely eligibility for SAVER will require an ***additional*** screening biopsy to be sent to the central laboratory in Newcastle. This is in order to confirm eligibility with the central pathology service, and this will additionally provide initial tissue to inform trial endpoints.

Patients who are potentially eligible who have ***not yet received a confirmed histopathological diagnosis*** (e.g. new referrals with clinically suspicious lesions) may have their diagnostic biopsy replaced by a SAVER screening biopsy. This will avoid the situation where a patient is subject to two invasive biopsies in quick succession i.e. 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 patient is ultimately recruited to the SAVER trial, all biopsy tissue is sent to Liverpool University GCP lab. If the patient does not enter the trial then the written report is sent to the recruiting site. If prior to this a request is made for return of the tissue to site, then the tissue will be sent directly to the site along with the report. If there is no prior request then this tissue will also be sent to Liverpool University GCP lab, if the site makes a subsequent request for the tissue then it will be returned from the GCP lab to the site according to standard laboratory procedures. 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 Informed Consent

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Written Informed consent is required for all patients participating in CTC coordinated trials. The process should involve discussion between the potential participant and an individual knowledgeable about the research, the presentation of written material (e.g. information leaflet or consent document), and the opportunity for potential participants to ask questions and have these satisfactorily answered. In obtaining and documenting consent, the research team 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. Informed consent should be re-affirmed throughout the trial and all discussions and consent should be documented appropriately. If a potential participant does not want to provide consent they do not have to give a reason.

Prospective Informed Consent Process

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. Appropriate Patient Information Sheets 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 documents. Upon reviewing the documents, 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.

6.3 Enrolment/ Baseline

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

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 may only be used for screening if performed within 90 days prior to randomisation

**An exception for this is only made for patients who underwent research biopsy under protocol 7, but did not proceed to randomisation due to suspension of trial recruitment. For such patients the 90 day limitation on their biopsy does not apply, however all other assessments other than the biopsy may only be used for screening if performed within 90 days of randomisation.*

Following biopsy eligibility confirmation the following screening/enrolment assessments should be performed:

1. Written Informed Consent (Main Trial)
2. Assessment of eligibility criteria
3. Review of medical history
4. Review of concomitant medications
5. BMI examination
6. Oral examination
7. Lesion measurement (with clinical photographs* and ruler at screening)
8. Haematology / clinical chemistry
9. EDTA blood sample for PWBC (to GCP Lab standard)
10. Research biopsy (5mm punch) (this will be split between GCP & Path labs by the trial pathologist)

* Clinical photographs will ideally be a single clear image, but two or three may be used for a complex lesion that demands differential angles to adequately capture (maximum 3 images).

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.

Screening & Eligibility and Pre-randomisation data will be entered into MACRO (a commercially available on-line research database system) by the research team at the recruiting site.

Once MACRO eligibility is confirmed and MACRO sign off completed by the Investigator at site, a Clinical Review will be performed by one of the Clinical Review Team.

When the Clinical Review is complete, randomisation will be processed by the Clinical Reviewer site using TARDIS.

A Randomisation Instruction Guide for Sites will be provided by LCTC.

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

Following successful randomisation a copy of the written Informed Consent Form should be uploaded to the LCTC portal or securely emailed to the LCTC SAVER trial team for verification.

LCTC CONTACT DETAILS

FOR RANDOMISATION QUERIES:

Tel: 0151 794 0260 or 0151 795 8577

Email: saver@liverpool.ac.uk

(Note that the LCTC is open from 09:00 – 17:00 Monday – Friday, excluding public holidays and University closed days)

7 TRIAL TREATMENT

7.1 Introduction

Patients will be randomised between Sodium Valproate Gastro resistant (Arm A) and a control group (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	500mg Gastro resistant tablets (not modified release)
Active Ingredient Name	Sodium valproate
Excipients	For a full list of excipients, see SmPC section 6.1 of the brand in use at your site
Prolonged release	No
Suppliers name	Site specific brand in use
Storage	Please refer to the SmPC of the brand in use at your site if tablets are in blisters

Sodium Valproate 500mg Gastro resistant tablets will be sourced from usual NHS hospital stock using generic brands prescribed within the NHS, unless advised otherwise by the trial pharmacist.

The hospital pharmacy will label the investigational medicinal product (IMP) in accordance with Annex 13 requirements/regulations* at the point of dispensing. IMP will be dispensed to the patient against a trial specific prescription issued by a delegated prescriber.

*EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines

Patients randomised to Arm A will receive 4 months of treatment, with a run-in period of Sodium Valporate Gastro resistant 500mg once each day for 14 days, increasing to 500mg twice a day thereafter.

On randomisation of a new patient, an automated email to confirm the randomisation details is generated. This is sent to SAVER trial team, PI and all relevant members of the site staff and pharmacy, notifying them of the patient trial number and treatment Arm.

Sodium Valporate Gastro resistant should be stored as per local practice and SmPC of the brand in use at your site.

Please refer to the SmPC of the brand in use at your site.
An example SmPC is available here http://emc.medicines.org.uk/

7.2.1 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 LCTC; however sites may use their own provided they have been approved by the study team.

The prescriber/pharmacist must ensure that all female patients have received the Patient Guide. They must ensure that Patient Card is provided with every valproate dispensation and that patients understand its content. These patient guide and patient cards are standard documents that are available to download from the eMC website: https://www.medicines.org.uk/emc/product/1446/rmms

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

7.2.2 Preparation, Dosage and Administration of Sodium valproate

Sodium valproate gastro resistant 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 gastro resistant 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.

7.2.3 Dose Modifications

Sodium valproate gastro resistant dose in SAVER trial is considered as 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). 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 after discussion with the CI.

7.3 Arm B

Patients in Arm B, the control arm of the trial will not receive any trial medications.

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 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.

7.5 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 gastro resistant administration, patients in Arm A 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 Gastro resistant tablets must be kept for inspection by the LCTC if required and shall only be destroyed with the written permission of the LCTC.

7.6 Concomitant Medications/Treatments

7.6.1 Overdose

Sodium valproate gastro resistant 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.

7.6.2 Medications Not Permitted

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

Antipsychotic and anticonvulsant medications

MAO Inhibitors

Antidepressants

Benzodiazepines

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

***Patients that are taking low doses of protein bound drugs, specifically 75mg Aspirin once daily, are eligible for inclusion in the SAVER trial.**

7.7 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 PARTICIPANT TIMELINES AND ASSESSMENTS

8.1 Schedule of Trial Procedures

				Treatment Visits/Calls						Follow-up			
Study Procedures		Screening*	Pre-Randomisation visit	Randomisation & 1st Trial Medication [1]	Unscheduled visit / biopsy [3]	1 month	2 month Visit ^	Unscheduled visit / biopsy [3]	3 month	4 month Visit ^	Unscheduled visit / biopsy [3]	6 month Visit ^	Unscheduled visit / biopsy [3]	End of Trial Data Collection
Signed Consent Form		X	X											
Assessment of Eligibility Criteria		X	X											
Review of Medical History		X	X											
Review of Concomitant Medications		X	X		X[3]		X^	X[3]		X^	X[3]	X^	X[3]	
Verbal Consent (Information Study contact)		X												
Telephone Consultation						X			X					
Study Intervention (0-4 months)				X[1]	X[3]		X^	X[3]		X^				
Risk exposure update (smoking and alcohol)		X			X[3]		X^	X[3]		X^	X[3]	X^	X[3]	
Examination	Body Mass Index	X	X							X				
	Oral Examination	X	X		X[3]		X^	X[3]		X^	X[3]	X^	X[3]	
	Lesion Measurement with Clinical Photographs & ruler (maximum 3 images)	X			X[3]			X[3]		X^				
Assessment of Adverse Events (LAEP Questionnaire – Appendix 3)			X				X^			X^		X^		
Clinical Laboratory^	LFTs & PT/APPT		X		X[3]		X^	X[3]		X^				
	Haematology: FBC		X		X[3]		X^	X[3]		X^				
Research Blood	EDTA sample for PWBC (The first of which to GCP Lab standard for subsequent AI studies)		X		X[3]		X^	X[3]		X^2				
	Plasma Sodium Valproate levels				X[3]		X^	X[3]		X^2				
Research Biopsy	FFPE 5mm punch biopsy	X			X[3]			X[3]		X^2	X[3]		X[3]	
FSH Test (female only)			X											
Dispense study drugs: Sodium Valproate Gastro resistant				X[1]			X^1							
End of Trial Data Collection														X[4]

			Treatment Visits/Calls							Follow-up			
Study Procedures	Screening*	Pre-Randomisation visit	Randomisation & 1st Trial Medication [1]	Unscheduled visit / biopsy [3]	1 month	2 month Visit ^	Unscheduled visit / biopsy [3]	3 month	4 month Visit ^	Unscheduled visit / biopsy [3]	6 month Visit ^	Unscheduled visit / biopsy [3]	End of Trial Data Collection

***** Screening and Pre-randomisation visits can be combined in one patient visit according to local practice

[1] Arm A patients only – issue of trial medication

[2] 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

[3] In the event of clinical concern regarding malignant transformation occurring other than at base line or 4 month timepoints an unscheduled biopsy may be carried out and additional samples taken – see section 8.4

[4] Case Note review at end of SAVER trial – see section 8.4.2

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. This measurement is made by a blinded central review panel. 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.

Assessment of histologic grading*: FFPE 5mm punch biopsy, bisected and stained with hematoxylin and eosin.

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

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^{o}C for 5 min, 25 cycles consisted of 94^{o}C for 30 sec, 55^{o}C for 30 sec, 72^{o}C for 45 sec, and a final extension step at 72^{o}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^{o}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)

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 surgical excisions and is not required prior to an incisional biopsy.

A standard pharmacovigilance programme will be set up. In the event of a SUSAR and in the event of the adverse event being judged to be due to SV, this will be reported to the MHRA in compliance with the clinical trial pharmacovigilance requirements. All SUSARs are managed in accordance with the LCTC Pharmacovigilance SOPs and the SAVER Pharmacovigilance plan. Assessment of AEs associated with sodium valproate gastro resistant 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 gastro resistant.

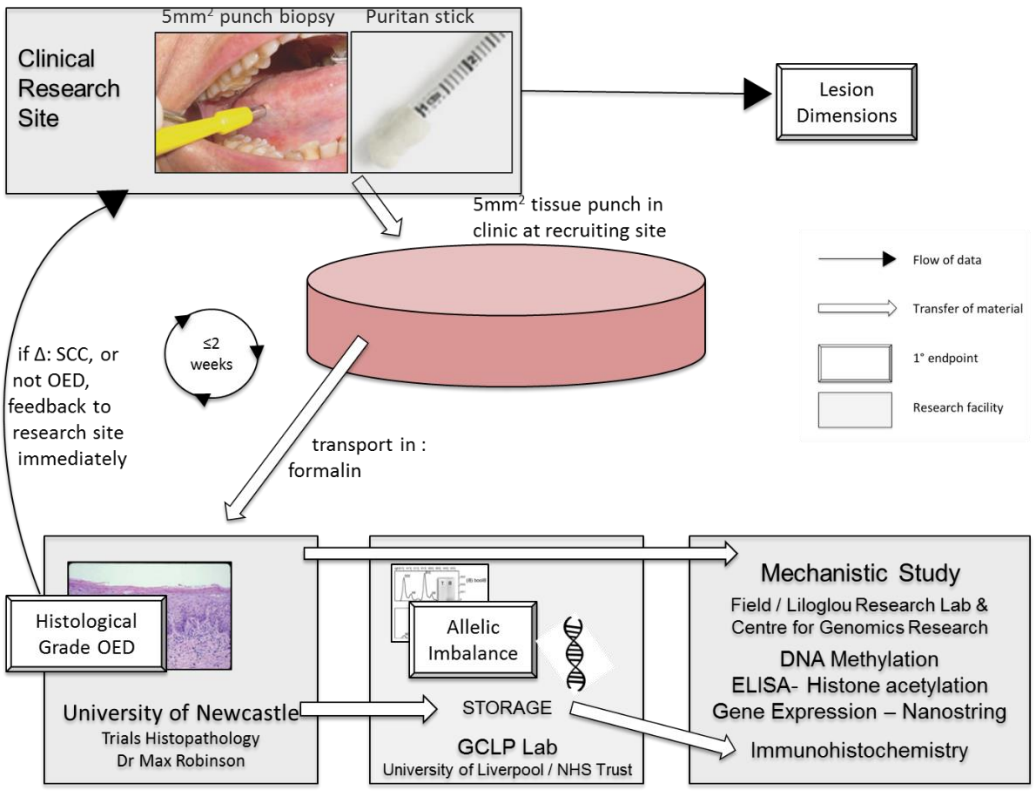
8.4 Assessments

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 GCP 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. In the event of clinical concern regarding malignant transformation occurring other than at baseline or 4-month timepoints, a clinical photograph with in-field Puritan stick and an urgent biopsy should be carried out (and additional samples taken as appropriate per 8.1 Schedule of Trial Procedures). This will be dealt with as a research biopsy at the clinical trial laboratory in Newcastle. In the event malignant transformation is diagnosed, the patient reaches their primary end point and is treated clinically as appropriate. In the event malignant transformation is not diagnosed the patient is retained on trial until the end point is reached.



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

8.4.2 End of Trial Data Collection

The trial duration is 6 months per subject but additional data on malignant transformation will be recorded at the end of trial by case note review

SAVER Trial Team will notify all sites when the 'End of Trial' timepoint is reached. A case note review should then be conducted to establish any new diagnosis of Oral Squamous Cell Carcinoma (OSCC).

MACRO page End of Trial > End of Trial Data Collection form should be completed at this time.

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.

8.5.1.3 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.

8.5.1.4 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.

8.5.1.5 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.

8.5.2.4 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 PISC 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.

8.5.2.5 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.

8.5.2.6 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.

8.5.2.7 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 randomised 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

A participant will be considered lost to follow up if they fail to return for scheduled visits and is not contactable by the site research team.

If a participant fails to attend/facilitate a required study visit the following actions must be taken:

- Site will attempt to contact the participant and reschedule the missed visit (be conscious of acceptable windows for collecting valid data) and advise the participant on the importance of maintaining the assigned visit schedule.
- Before a participant is deemed to be lost to follow up, site research staff will make every effort to regain contact with the participant (i.e. telephone calls and, if necessary, a headed letter to last known address). These efforts should be recorded in the patient medical notes.
- If the participant continues to be unreachable they should be considered withdrawn from the study with a primary reason of lost to follow up and this should be recorded on the appropriate CRF.

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 (the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database).

Site and closure activities will be centrally coordinated and conducted in accordance with CTU processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC and competent authority e.g. MHRA.
- Trial-related materials reconciled and returned/disposed of as appropriate see section 7 for IMP
- All site data entered onto the study database, discrepancies raised and satisfactory responses received
- Quality Control checks of the Investigator Site Files, Pharmacy Files and Trial Master File as appropriate.

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

This section provides an overview of all statistical aspects of the study relating to SAVER: A controlled randomised (1 active observation only:2 SV), multi-centre phase II clinical trial investigating the use of sodium valproate gastro resistant 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 an independent LCTC 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 the estimated elliptical area given by the longest length of the lesion and the associated perpendicular width.

$$\pi(\text{radius a X radius b})$$

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 be used 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 responsiveness 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 trial biopsies and also within the 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.
- 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.
- 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 after the last patient randomized completes 6 months follow-up.
- 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 on active observation only 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 $p_0 = 0.2$, 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 active observation only 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, based on 10 or more sites recruiting at an average rate of 0.4 patients per site per month (~ 4 patients per month).

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. It will be the job of the ISDMC to assess the feasibility of the study and to make appropriate recommendations to the TSC.

The main feasibility outcome is recruitment rate. Targets for recruitment will be set at 43 and 88 for 12 and 24 months respectively. As a guide, it is proposed that if the study will be recruiting within 80% of the intended rate (at least 34 and 70 for 12 and 24 months respectively) then no action will be taken. If the study is recruiting between 50% and 80% (between 22-33 and 44-69 for 12 and 24 months respectively) of the intended rate, the ISDMC may recommend continuation only if strategies will be put in place to increase recruitment. If the study is recruiting at less than 50% (less than 22 and 44 for 12 and 24 months respectively) of the intended rate, 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 completed a follow up visit at 6 months post treatment.

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. A sensitivity analysis of the primary outcome will be performed on the primary outcome removing lesion size. Toxicity analysis will be carried out on the basis of which arm patients were actually allocated to.

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 gastro resistant to active observation only. 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, where possible, shall mirror that of the primary analyses, using stratified Mantel Haenszel test and multivariable logistic regression techniques.

Analyses of time to event 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 SAFETY REPORTING (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 Serious Adverse Reaction (SUSAR)

An adverse reaction that is classed in nature as serious and "unexpected" (i.e. not listed within the Reference Safety Information (RSI) approved for the trial by the MHRA and current at the time of onset of the SUSAR).

Reference Safety Information (RSI)

The information used for assessing whether an adverse reaction is expected (see section 10.6) This is contained in the Summary of Product Characteristics (SmPC) or Investigators Brochure (IB) for the product and must be approved for use by the MHRA. The RSI used to assess the expectedness of a SAR must be the current approved version at the time of onset of the SAR. The RSI for this trial is defined in section 10.6

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

Pregnancy is not expected as women of child bearing potential are excluded from the SAVER Trial. Despite strict eligibility criteria, if patients become pregnant while receiving trial treatment within Arm A, they must immediately discontinue said treatment.

If a patient within Arm A 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 reported to the LCTC **within 24 hours** of learning of its occurrence.

On pregnancy outcome, the final Pregnancy Report Form should be reported to the LCTC 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 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.

Report events & outcomes by secure email to:

Liverpool Clinical Trials Centre

Email: lctcsafe@liverpool.ac.uk

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 LCTC 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:

Table A: Severity Grading

Severity	Description
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
Unrelated	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

The Chief Investigator for the SAVER trial is responsible for determining whether a safety event is expected or unexpected, however a Chief Investigator will not assess their own patients, these patients will be assessed by the Medical Reviewer/Clinical Coordinator. There is no requirement for a reporting investigator to make an assessment of expectedness.

An event will be considered unexpected if it is not listed within the current and approved RSI (see section 10.6) for the study at the time of the event's onset. The nature, severity, or frequency of the event should be considered – if this is not consistent with that described for the type of event in the RSI the event should be assessed as unexpected.

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 taken from the eMC.

The RSI document is for the assessment of Adverse Events ONLY. Management of the IMP products should be conducted in accordance with the current SmPC of the brand in use at your site as it is updated throughout the life cycle of the study (see section 7. Trial Treatments).

10.7 Time Period for Active Monitoring of Safety Events

IMPORTANT: Any safety events occurring after the end of the below described "active monitoring" period which meet the definition of serious (see section 10.1) and are recorded for this study (see section 10.2) must continue to be reported by sites to the LCTC in accordance with the timeframes and procedures described in section 10.9. The same processes established for SAEs within the active monitoring period should be followed for these events.

Active monitoring of safety events experienced by trial participants will be from the period of randomisation until to 6 month appointment / 6 month visit whichever is sooner with the exception of any malignant transformation or new head and neck cancer, which should be collected until trial closure.

10.8 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.

10.9 Reporting Procedures

All safety events which are recorded for the study should be reported following the procedures detailed below. The occurrence of a safety event may come to the attention of research staff during routine study visits, from the participant's notes, directly from the participant or by other means. Note that reporting procedures vary dependent on the nature of the incident (i.e. "serious" events are to be reported to LCTC in an expedited manner). Any questions concerning adverse event reporting should be directed to the LCTC in the first instance. A flowchart is given below to aid in determining reporting procedures for different types of adverse events.

Adverse event reporting is the same for both Arms.

10.9.1 Non-serious ARs/AEs

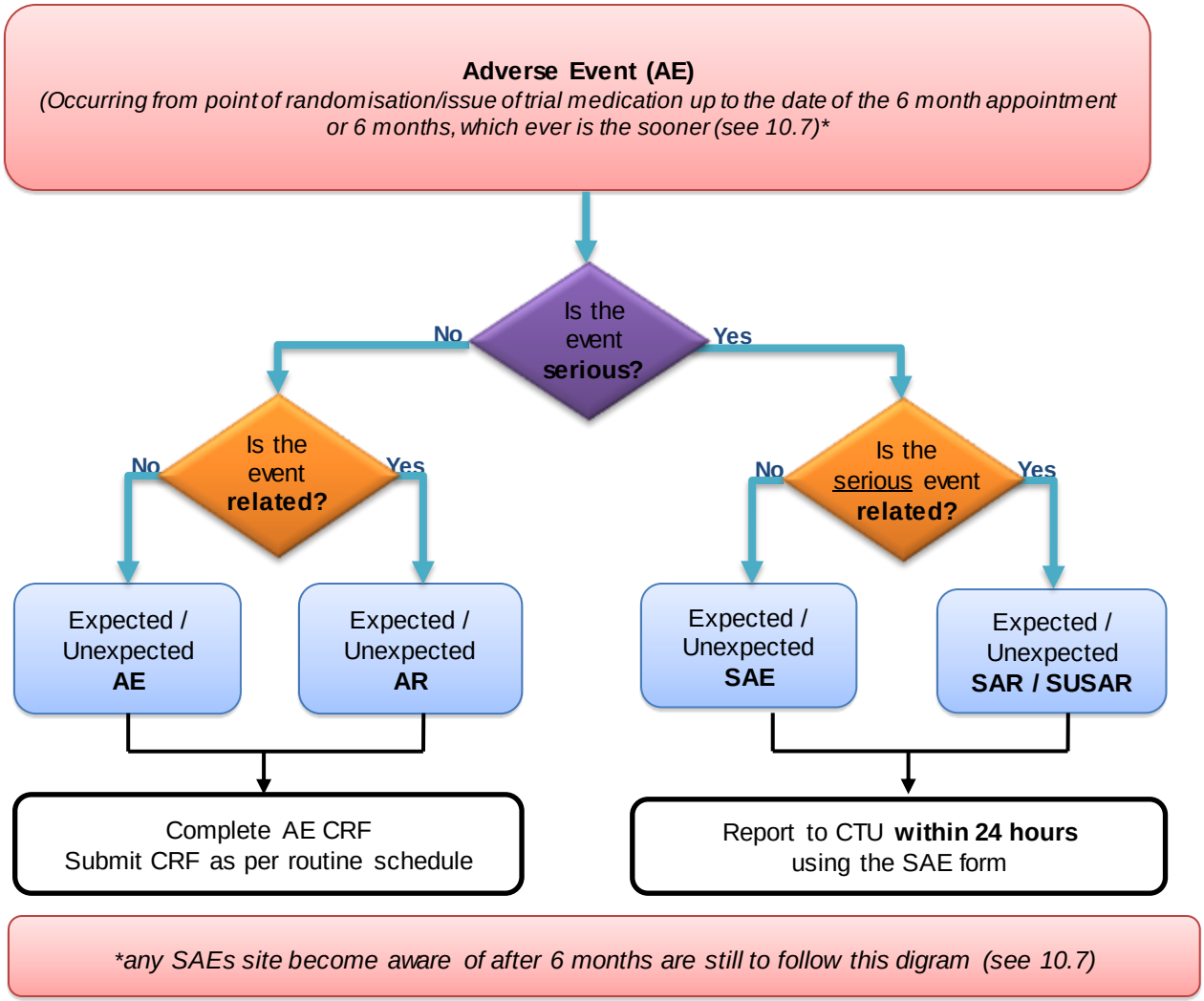
All such events, whether expected or not, should be recorded in the relevant page of the CRF.

10.9.2 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 LCTC 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.

10.9.3 Flowchart for Site Reporting Requirements of Adverse Events



10.10 Responsibilities – Investigator

The PI is responsible for ensuring that all safety events requiring recording on this study (see section 10.2) which the local research team becomes aware of are reported to LCTC. It is the responsibility of the PI/Co-PI as recorded on the Delegation Log (medically qualified person) to assess the seriousness and causality of events. When documenting any adverse events, the correct medical terminology **must** be used in accordance with CTCAE.

All safety events must be recorded on an AE form and transferred to LCTC **within seven days of the site team becoming aware of the event**.

Safety events which meet the definition of "serious" must be reported in more detail to the LCTC on an SAE form and reported **immediately and in no circumstances later than 24 hours from becoming aware** unless the SAE is specified in the protocol as not requiring immediate reporting where they will be appropriately processed.

The SAE form should be completed by an appropriately delegated member of the research team; the assessments of seriousness and causality must be performed by an appropriately medically qualified person/dentist. Minimum reporting information must be provided in initial reports for all studies.

N.B. In the absence of a delegated medically qualified person/dentist, the form should be completed and signed by an alternative member of the research site trial team and submitted to the LCTC. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the LCTC. The initial report shall be followed by detailed follow-up reports as appropriate.

Safety events should be reported to the site R&D team in accordance with local policy

Minimum information required for reporting:

- Study identifier
- Study centre
- Patient number (Trial Number)
- A description of the event
- Date of onset
- 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 securely transferred to the LCTC immediately. The responsible investigator should check the SAE form, make changes as appropriate, sign and then re-transfer to the LCTC as soon as possible. The initial report shall be followed by detailed, written reports.

ii. Send the SAE form by secure email (within 24 hours or next working day) to the LCTC

Completed SAE Reports must be reported
within 24 hours of becoming aware of the event to
the Liverpool Clinical Trials Centre

Email: lctcsafe@liverpool.ac.uk

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 LCTC 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, month and year of birth and initials only. The patient's name **should not** be used on any correspondence.

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.

10.11 Responsibilities – LCTC

The trial Sponsor, University of Liverpool, have delegated to LCTC the duty of onward reporting of safety events to REC, regulatory authorities (MHRA, competent authorities of other European member states in which the trial is taking place). SOPs will be followed to ensure appropriate reporting as detailed below.

Safety events which are assessed as "serious", "related" and "unexpected" will be expedited to relevant REC and applicable regulators, e.g. MHRA as a SUSAR within the following timeframes:

- SUSARs which are fatal or life-threatening – **as soon as possible and in any case no later than 7 days** after the LCTC is first aware of the event. If the initial report is incomplete, a complete report will be submitted within an additional 8 days.

- SUSARs that are not fatal or life-threatening – **within 15 days** of the LCTC first becoming aware of the event.

Additionally, SUSARs will be reported to the trial Sponsor and Principal Investigators of participating sites and other third parties as applicable within the agreed timelines.

The LCTC will submit an Annual Safety Report to REC and a Development Safety Update Report to the MHRA on an annual basis.

The PIs at all institutions participating in the trial will be notified of any SUSARs within a reasonable timeline.

Any concerns raised by the TSC/ISDMC or inconsistencies regarding safety reporting noted at a given site may prompt additional training at sites, with the potential for the LCTC to carry out site visits if there is suspicion of unreported AEs / ARs and SARs / SAEs in patient case notes. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

10.11.1 Safety Reports

If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified

10.11.2 Urgent Safety Measures (USMs)

An urgent safety measure (USM) is a procedure to protect clinical trial participants from any immediate hazard to their health and safety but has not previously been defined by the protocol. It can be put in place prior to authorisation by the REC and the MHRA.

The Sponsor/LCTC will notify the MHRA and REC immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the REC and MHRA will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the REC and MHRA, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

Following notification, if a substantial amendment is required this must be submitted as soon as possible to the REC and ideally within two weeks to the MHRA. If the study is temporarily halted it may not recommence until authorised to do so by the REC and MHRA. If the study is permanently terminated before the date specified for its conclusion (in the original applications to REC and MHRA), the Sponsor should notify the REC and MHRA within 15 days of the date of termination by submitting the formal End of Trial Notification.

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.

11.2 Ethical Approval

The trial will abide by the principles of the World Medical Association Declaration of Helsinki and has been designed to be as pragmatic as possible. The protocol has undergone ethical review by an independent Research Ethics Committee and has received a favourable opinion.

11.3 Approvals

The protocol, PIS, ICF and any proposed public-facing material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), Health Research Authority (HRA) and host institution(s) for written approval.
Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

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 LCTC before patients are entered. The LCTC should receive notification of positive capacity and capability for each new centre via the site's R&D department.

11.4 Protocol Deviation and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and relevant regulatory and ethical e.g. MHRA and REC requirements are handled based on their nature and severity.

11.4.1 Non-Serious breaches

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and LCTC procedures as appropriate. They will be reported to trial oversight committees.

11.4.2 Serious breaches

A breach of the protocol or GCP is 'serious' if it meets the definition of being "likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial". This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a 'serious' breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC and TSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants. The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as 'serious' will be reported to MHRA and REC within 7 days by the CTU on behalf of the Sponsor and notified to the TMG, ISDMC and TSC at their next meeting.
Any requests for additional information from the Sponsor, TMG, TSC, ISDMC, MHRA, or REC, will be promptly actioned by the relevant member(s) of the research team and open

communication will be maintained to ensure appropriate corrective actions are taken and documented.
Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

11.5 Study Discontinuation

In the event that the study is discontinued, there are no provisions for patients 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 04196/0048/001-0001.

13 DATA MANAGEMENT AND TRIAL MONITORING

For the SAVER trial the responsibilities for Data Management and Monitoring are delegated to the LCTC. Separate Data Management and Trial Monitoring Plans provide detail regarding the internal processes that will be conducted at the LCTC throughout the trial.

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.

The trial will be centrally monitored and on-site monitoring will only be triggered if deemed necessary by the SAVER Trial Management Group.

13.1 Risk Assessment

In accordance with the LCTC Standard Operating Procedure a risk assessment was completed in partnership with the following:

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

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

The outcome of the risk assessment was 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 Gastro resistant 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

13.3.1 Case Report Forms

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

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

Trial data will be captured using remote data entry at research sites which will be entered onto the MACRO database by site staff at participating sites on electronic Case Report Form (eCRF), with the exception of adverse event reporting which will be processed on paper CRF (pCRF).

- 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.

A guide for entering data on MACRO will be available in the Portal Investigator Site File section and training will be given to delegated staff at the Site Initiation Visit.

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

13.4 Monitoring at LCTC

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

The Green Light Process in place at the LCTC 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.

Central Monitoring
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. 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.

Data will be entered into a validated database and during data processing there will be checks for missing or unusual values (range checks) and for consistency within participants over time. Other data checks relevant to patient rights and safety will also be regularly performed as per CTU processes. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the CTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to the CTU. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database.

Site monitoring visits may be 'triggered' in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

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. In agreeing to participate in this study, a PI grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the study protocol;
- discussing any emerging problems that may have been identified prior to the visit;
- checking CRF and query completion practices.

13.5.2 Confidentiality

This trial will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the trial (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

Case report forms will be labelled with patient initials and unique trial randomisation number. Tissue samples will be transferred to both the pathology and GCP laboratories and will be identifiable by unique trial randomisation number only.
Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to the CTU by recruiting sites. This transfer of identifiable data is disclosed in the PIS/IC.

N.B. Consent forms must be transferred separately to any other trial documentation to ensure the pseudonymisation of special category data is maintained.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study. The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

Breaches of data protection principles or regulations identified by LCTC will be notified promptly to the trial Sponsor and The University of Liverpool's Data Protection Officer and appropriate processes followed.

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 LCTC. Such audits/inspections may take place at any sites where trial related activity is taking place (i.e. the Sponsor site(s), Liverpool Clinical Trials Centre 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 LCTC 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 LCTC.

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 LCTC 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.

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties (e.g. laboratories, etc.).

The LCTC 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/LCTC will be responsible for the destruction of all trial related materials retained by the Sponsor/LCTC.

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

14 INDEMNITY

The University of Liverpool holds insurance against claims from participants for harm caused by their participation in this clinical study. However, the treating hospital continues to have a duty of care to the participant and the Sponsor does not accept liability for any breach in the hospital's duty of care, or any negligence of the part of hospital employees. In these cases, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

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

This study is an academic lead study that has been costed in accordance with DOH guidelines: Attributing the costs of health & social care Research & Development (AcoRD). There will be a per patient payment payable to centres to cover the patient specific research costs. Details of this payment are covered in the Research Site Agreement. Finite travel costs are available to patients to cover travel expenses incurred in attending hospital for the non-routine visits. The study has been adopted by the National Institute for Health Research Clinical Research Network (NIHR CRN) and UK Clinical Research Network (UKCRN).

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 LCTC. 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 LCTC.

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 AND DISSEMINATION

The results from different participating sites will be analysed together and published as soon as possible maintaining participant confidentiality at all times. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group (TMG).

The TMG 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 as a minimum. 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 and members of the TSC and ISDMC should be acknowledged.

17.1 Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and submitted to the MHRA and REC. The results of SAVER will be published regardless of the magnitude or direction of effect.

17.2 Data Sharing

At the end of the trial, after the primary results have been published, all requests for access to the IPD will be reviewed by an internal committee at the CTU and discussed with the Chief Investigator in accordance with the CTU policy on data sharing.

18 CHRONOLOGY OF PROTOCOL AMENDMENTS

18.1 Version 10 (June 2022) – current version

Summary of Amendments from Protocol V9.0 to Protocol V10.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
n/a	Cover Sheet & Contact Details	Update to contact details
n/a	All sections	Correction of grammar and typographical errors
4	Study Design	4.2 End of Study Definition - remove original definition (updated with protocol v9)
5	Eligibility Criteria	5.2 Exclusion Criteria updated: 6. A patient who has received sodium valproate medication within the last 10 years 7. Epilepsy that has led to the use of any antiepileptic therapy within the last 10 years 8. Obesity (Body Mass Index >= 35) 9. Known relative or absolute contraindications to Sodium Valproate (as listed in British National Formulary), and specifically: c. Personal or family history of severe hepatic dysfunction, as defined by Child-Pugh Group C (see appendix 4) d. current hepatic dysfunction (as evidenced by LFTs significantly outwith reference range or prolonged prothrombin time) f. Women with child-bearing potential. A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Women who have undergone total hysterectomy or bilateral salpingo-oophorectomy or who are in a postmenopausal state are eligible for the SAVER trial. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range will be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). Females on HRT must discontinue HRT to allow confirmation of postmenopausal status before study enrolment. Otherwise, they must be considered non-eligible to participate in this trial and excluded.
6	Enrolment and Randomisation	6.3 Enrolment/Baseline - clarification of main trial randomisation assessments (following biopsy eligibility confirmation)

8	Participant Timelines and Assessments	8.1 Schedule of Trial Procedures updated/added: • Telephone consultation at 1 & 3 months • Body Mass Index increased to >=35 • Clinical Photographs (preferably 3 images) • End of Trial Data Collection Case Note review • Activity divided into Treatment Visits/Calls and Follow-up 8.4.2 End of Trial Data Collection added
9	Statistical Considerations	9.3.1 Assessment of lesion size clarified 9.5 Study Recruitment Projection - graph deleted 9.8.1 Timing of analysis clarified
18	Chronology of Protocol Amendments	Changed to Table format to include a summary of change
20	Appendices	Appendix 4: COVID-19 SAVER MHRA Risk Assessment Statement Appendix 5: The Child-Pugh classification

18.2 Version 9 (March 2021)

Summary of Amendments from Protocol V8.0 to Protocol V9.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
6	Enrolment and Randomisation	6.3 Enrolment/Baseline Randomisation data to be entered by research site teams Randomisation to be processed by Clinical Reviewers
8	Participant Timelines and Assessments	8.1 Baseline LAEP Questionnaire added
10	Safety Reporting Pharmacovigilance	10.0 Update to LCTC Safety Reporting email address and fax machine numbers deleted 10.4 Definition of causality updated 10.7 new section: Time period for Active Monitoring 10.9 Reporting Procedures updated 10.10 Unnecessary references deleted Minimum reporting information updated Email address for safety reporting changed Patient identifier replaced with Month & Year of birth 10.11 non-CTIMP definitions and duplications deleted
13	Data Management and Trial Monitoring	13 Data Management and Trial Monitoring updated 13.4 Monitoring at LCTC 13.5.1 Direct Access to Data

		13.5.2 Confidentiality 13.5.4 Records Retention
18	Chronology of Protocol Amendments	Changed to Table format to include a summary of change

18.3 Version 8 (01 February 2021)

Superseded by Version 9. (Version 8 was not implemented in the trial).

Summary of Amendments from Protocol V7.0 to Protocol V8.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
Revised Protocol Template	All sections reviewed	SAVER trial re-design from double-blinded randomised trial with IMP/Placebo to unblinded randomised trial with IMP/observational control arm (no treatment). The modified trial design is unblinded, therefore both patients and site PIs will be unblinded as to allocation. Patients allocated to intervention arm will received Sodium Valproate 500mg as per protocol 7, but those allocated to control arm will not receive any medication. (In previous protocols, control arm patients received placebo). Oral Lichen Planus (within the lesion itself) deleted from exclusion criteria No changes to inclusion, randomisation, primary or secondary trial endpoints. New Appendices: Blinded trial design and Unblinding Information COVID-19 SAVER Recruitment Policy General administrative changes: Change to named Sponsor Representative; Changes LCTC named trial management staff; Address of Medical Expert for SAE evaluation

18.4 Version 7 (11 March 2020)

Summary of Amendments from Protocol V6.0 to Protocol V7.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
All sections reviewed	All sections reviewed	Inclusion and exclusion criteria updated to ensure ONLY women who are in a postmenopausal state are included in the trial and those with childbearing potential are excluded from the trial. Requirement of blood and urine pregnancy test (for WOCBP only) prior to trial medication replaced with the requirement of FSH test at the pre-randomisation visit for female patients. The SOP for women of childbearing potential has been removed from the protocol as it is no longer applicable as these group of women are excluded from the trial.

18.5 Version 6 (07 January 2020) Superseded by version 7 (Version 6 was not implemented in the trial).

Summary of Amendments from Protocol V5.0 to Protocol V6.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
All sections reviewed	All sections reviewed	Mainly update to include patients taking 75mg Aspirin as an inclusion criteria. Clarification of processes throughout the protocol including screening and enrolment processes, prescribing and distribution of Sodium valproate, assessment of SAEs in relation to placebos. General administrative changes: Addition of site contact details Merger of Liverpool Clinical Trials Centre (LCTC)

18.6 Version 5 (01 February 2019)

Summary of Amendments from Protocol V4.0 to Protocol V5.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
All sections reviewed	All sections reviewed	**Section 8.1: Schedule of Trial Procedures:** Clarification of Pre-randomisation visit and renaming of baseline visit to First issue of trial medication (see tracked changes in the protocol) **Section 9.2 Method of randomisation:** The sequences of allocation will be centrally generated by an independent LCTU statistician using the Stata package *ralloc* employing permutated block randomisation with variable block size of 3 and 6. **Section 9.3.1 Primary outcome measures: Assessment of lesion size:** N/A (deleted) **Section 9.3.2: Secondary outcome measures:** a. WHO grade of OED (or SCC) in trial biopsies and also within the entire whole resection specimen (where any oral resection is performed within trial period). b. 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. c. 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. **Section 9.5 Study recruitment:** The intent of the study is to recruit the 110 patients required over a period of 32 months. Recruitment estimates are based on 10 sites recruiting at an average rate of 0.4 patients per site per month (~ 4 patients per month). It is further expected that the first 5 sites will be open to recruitment in the first

		month and the further 5 at a rate of one per month. Please see tracked changes for the new recruitment projection graph. **Section 9.7 Internal feasibility study:** The main feasibility outcome of interest is the recruitment rate. Targets for recruitment are set at 36 and 80 patients for 12 and 24 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 29 and 64 patients for 12 and 24 months respectively) then no action will be taken. If the study is recruiting between 50% and 80% of the intended rate (18-28 and 40-63 patients for 12 and 24 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). **Section 9.8.6: Analysis of Secondary Endpoints**: Analyses of the categorical secondary endpoints, were possible, shall mirror that of the primary analyses, using stratified Mantel Haenszel test and multivariable logistic regression techniques. Analyses of time to event shall be carried out using stratified log rank test for comparisons across treatment groups. **Section 10.8 Reporting Procedures:** All adverse events that occur from the point of the patient's written informed consent are to be reported, even if the patient has not started taking the sodium valproate.

18.7 Version 4 (03 July 2018)

Original Approved version

18.8 Version 3 (17 May 2018)

18.9 Version 2 (16 April 2018)

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20 APPENDICES

Appendix 1: 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

Appendix 2: Blinded Trial Design and Unblinding Information (applicable to protocol versions 1-7 only)

1 Overall Design

SAVER trial was originally designed as a randomised, double-blind and placebo-controlled trial 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).
The trial opened to recruitment on protocol version 3 dated 17-May-2018 and closed to recruitment on protocol version 7 dated 11-Mar-2020.

A total of 9 participants were recruited to the original blinded design.
The last randomisation to the original blinded design was on 08-Sept-2020.

2 Patient transfer and withdrawal

Withdrawal from Trial Intervention

a. **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).
b. 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.

3 Blinding and Unblinding:

Prior to protocol version 8 SAVER was 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 LCTC IT representative, Monitors and unblinded Trial Coordinators) will remain blinded with regard to the randomised treatment allocations for patients recruited under protocols 1-7.

Blinding for the SAVER trial has been 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.

4 Procedures for Assessing Safety

A standard pharmacovigilance programme has been set up. In the event of a SUSAR, the subject recruited under protocol 1-7 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 in compliance with the clinical trial pharmacovigilance requirements.

5 Pharmacovigilance: 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.

6 Reference Safety Information

There is no RSI in place for the trial placebo. Therefore, any serious adverse events assessed as having a causal relationship with the placebo will be considered as unexpected and reported in accordance with Section 10.8.2 Serious Ars/AEs/SUSARs.

Appendix 3: COVID-19 SAVER Recruitment Policy - September 2020

Background:
Recruitment to SAVER had been paused at sites during the peak of the COVID-19 pandemic, as has recruitment to most other cancer trials. As the UK and international sites start to plan an effective recovery from COVID-19 disruption, there will be a need to balance the continuing risks relating to COVID-19 infection with the need to resume 'normal' activity and to provide patients with optimal care in the safest possible environment. Clinical trials will need to be reactivated in a phased and risk-adapted way during this recovery period.

Re-starting recruitment to SAVER has potential merit in the COVID-19 era, because it is a cancer prevention clinical trial. Patients eligible for SAVER have high-risk premalignant lesions and therefore will be a group where clinical examination and face to face appointments will continue to be necessary. The balance of risks of malignant transformation and resultant tumours will, naturally, be weighed carefully against the risks inherent in travel and attendance at hospitals.

The SAVER Chief Investigator and Trial Management Group have discussed and agreed the following framework within which recruitment can commence/re-commence at sites.

Eligibility: No changes are proposed to study eligibility criteria, however patients who are currently COVID-19 positive should not be approached for the study. In contrast, patients who have previously contracted COVID-19 and have recovered to the extent that they are considered fit for surgery and trial interventions as per protocol are eligible for registration.

Consent: Patients being registered for the SAVER study need to be informed by their clinical teams about the extra risks potentially associated with COVID-19, as they would before any cancer or pre-cancer treatment in the COVID-19 era.

Surgery: Published data confirm that for surgical patients who develop COVID 19 in the perioperative period, mortality rate is increased significantly (1). It is therefore imperative that the risk of any patient undergoing surgery whilst asymptomatically infected with COVID-19, or becoming infected in the post-operative period, is reduced as far as practically possible in order to reduce the risks to patients as well as the risk to healthcare workers of becoming infected.

COVID-19 has an incubation period of 1-14 days (median 5 days). Median time from onset of symptoms to clinical recovery is 2 weeks in mild cases and 3-6 weeks in severe or critical cases.

For patients undergoing surgery as part of the SAVER protocol, the following precautions are now mandated, as a minimum, in line with recommendations from the Royal College of Surgeons (England), data from the COVIDsurg cohort studies (2), and ENT-UK (3). These requirements will apply to those having definitive resection of lesions at 4 months under general anaesthetic, and will not be relevant to patients being managed with surveillance.

- All patients recruited to SAVER should have their surgery in a designated COVID-Free environment, as defined by local service configuration and clinical practice.

- COVID-19 PCR swab testing should take place 24 to 72 hours prior to surgery. The operating surgeon is responsible for ensuring the test result is negative BEFORE embarking on surgery.
- Surgery should only proceed if the swab test is negative and the patient is asymptomatic for COVID-19 and apyrexial on the day of surgery.

Peri-operatively and post-operatively, the risk of COVID-19 infection to patients and staff should be minimised, through use of appropriate Personal Protective Equipment (PPE) by healthcare workers, implementing best practices and limiting visitors to the ward, as per local standard protocols.

Patients having local anaesthetic biopsy as part of the SAVER protocol are not subject to such strict criteria. For these procedures, patients are not required to undertake PCR testing and correspondingly are not managed in a designated COVID-free environment as these are minor outpatient attendances. For such procedures, it is assumed that local guidelines will ensure:

- Biopsy should only proceed if the patient is asymptomatic for COVID-19 and apyrexial on the day of surgery.
- Appropriate PPE is used through this procedure, usually consisting FFP3 mask, eye protection, disposable gloves and gown.

Patients who test positive for COVID-19 on the SAVER study:

Patients who test POSITIVE on SARS-CoV-2 PCR swab testing 24-72hrs prior to any surgery / biopsy or randomisation must have their surgery or randomisation delayed for at least 2 weeks, or full recovery from any associated illness (whichever is later) and also in line with local protocols. Please submit an SAE form stating that the patient was 'positive for COVID-19'.
Patients who test positive for COVID-19 on trial, after randomisation should continue on the study subject to ongoing assessment of their medical fitness. Please submit an SAE form stating that the patient was 'positive for COVID-19'.

FOLLOW-UP:

It is likely that Centres may wish to reduce the number of face-to-face follow-up visits for all patients including those enrolled-on SAVER, and that communication with patients can continue by telephone wherever possible.

References

(1)Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. COVIDSurg Collaborative. Lancet. 2020 Jul 4;396(10243):27-38. doi: 10.1016/S0140-6736(20)31182-X.

(2)Elective cancer surgery in COVID-19 free surgical pathways during the SARS-CoV-2 pandemic: An international, multi-centre, comparative cohort study. 2020. COVIDSurg Collaborative. *J Clin Oncol 2020* [accepted ahead of print]

*(3)*ENT UK - Consent and Pre-operative Assessment for ENT surgery: A Graduated Return to Elective ENT within the COVID-19 Pandemic.

Appendix 4: COVID-19 SAVER MHRA Risk Assessment Statement

COVID-19 vaccine given to a trial subject is considered as a simple concomitant medication with no interaction that requires advice on timing of the vaccine or other aspects.

Appendix 5: The Child-Pugh classification

The Child-Pugh classification

Assessment	Degree of abnormality	Score
Encephalopathy	None Moderate Severe	1 2 3
Ascites	Absent Slight Moderate	1 2 3
Bilirubin (mg/dL)	<2 2.1-3 >3	1 2 3
Albumin (g/dL)	>3.5 2.8-3.5 <2.8	1 2 3
Prothrombin Time (seconds > control)	0-3.9 4-6 >6	1 2 3

Total Score	Group	Severity
5-6	A	Mild
7-9	B	Moderate
10-15	C	Severe