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Sodium valproate for epigenetic reprogramming in the management of high risk oral epithelial dysplasia

Submission date 23/04/2018	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol
Registration date 24/04/2018	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 17/11/2025	**Condition category** Oral Health	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims
People can develop patches (oral dysplasia) on the lining of the mouth which are at risk of developing into cancer. Standard treatments include surgery or close surveillance, although these treatments are not completely effective, as up to 25% of patients progress to oral cancer even after surgery. Oral cancer treatments can be curative, especially when caught early, but the side effects include damage to speech, swallowing, appearance and reduction in quality of life, which are permanent. Treatment for oral cancer also carries a high economic burden and the World Health Organisation has recommended a shift in policy towards early diagnosis and prevention. Survival rates for oral cancer have remained largely unchanged for decades, at around 50-55% overall survival by 5 years. There is therefore a need to develop and test new prevention treatments for this condition. It is thought that more effective treatment for oral dysplasia would reduce the incidence of oral cancer. This study aims to investigate the effects of the drug sodium valproate as a preventative treatment for high-risk oral dysplasia, in order to inform a decision on a larger study.

Who can participate?
Patients aged 55 years old and over with high-risk oral epithelial dysplasia

What does the study involve?
Participants are randomly allocated to take either sodium valproate or placebo (dummy drug) tablets twice daily for 4 months or to an observational control arm will no medication. Measurements, photographs and punch biopsy tissue samples are taken at the start of the study and after 4 months to assess the response to treatment.

What are the possible benefits and risks of participating?
It is hoped that the treatments will help patients. However, this cannot be guaranteed. The information from this study may help to improve the future treatment of patients who have oral dysplasia. As part of the study patients may have one extra biopsy in addition to the normal care needed. These biopsies involve removing a small, 5 millimetre, disc of tissue. They can be carried out under local anaesthetic, using a small injection to make that area numb and will usually need

one or two dissolving stitches. The risks of oral biopsy include some pain which might last up to one week, and a small amount of bleeding although this is likely to be only minor. Patients will also receive blood tests on three occasions that will not normally be needed unless on the study. Sodium valproate may have side effects but at the dose used in the study side effects are not expected in most patients. Sodium valproate can cause some people to put on weight. Other side effects that are usually seen at higher doses (and should be rare in this study) include tremor, drowsiness and mental slowing. Other very rare side effects include damage to the liver and changes to blood cells but these are checked carefully during the study using blood tests. Whether in the study or not, the patients' oral dysplasia might worsen or even change to cancer, but patients will be very carefully monitored. Being on the study will not alter treatment decisions, and if patients' doctors feel they need a different treatment at any point, this will be offered as standard.

Where is the study run from?
1. Liverpool University Dental Hospital (UK)
2. Aintree University Hospital NHS Foundation Trust (UK)
3. Leeds Dental Institute (UK)
4. Eastman Dental Institute and Hospital (UK)
5. KCL Dental Institute (UK)
6. Charles Clifford Dental Hospital (UK)
7. Royal Blackburn Hospital (UK)
8. Queen Victoria Hospital (UK)
9. Sunderland Royal Hospital (UK)
10. Bristol Dental Hospital (UK)
11. Glasgow Queen Elizabeth Hospital (UK)
12. Aberdeen Royal Infirmary (UK)

When is the study starting and how long is it expected to run for?
January 2018 to September 2026

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
1. SAVER Trial Inbox
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2. Albert Jimenez-Tomas (Trial Manager)
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3. Prof. Richard Shaw (Chief Investigator)
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Contact information

Type(s)
Scientific

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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2018-000197-30

Integrated Research Application System (IRAS)
236218

ClinicalTrials.gov (NCT)
Nil known

Central Portfolio Management System (CPMS)
CPMS 37192

Study information

Scientific Title
Sodium valproate for epigenetic reprogramming in the management of high risk oral epithelial dysplasia

Acronym
SAVER

Study objectives
Current study hypothesis as of 10/07/2024:
Individuals can develop patches (oral dysplasia) on the lining of the mouth which are at risk of developing into cancer. Standard treatments include surgery or close surveillance, although these treatments are not completely effective, as up to 25% of patients progress to oral cancer even after surgery. Oral cancer treatments can be curative, especially when caught early, but the side effects include damage to speech, swallowing, appearance and reduction in quality of life, which are permanent. Additionally, treatment for oral cancer carries a high economic burden and the World Health Organisation has recommended a shift in policy towards early diagnosis and prevention. Survival rates for oral cancer have remained largely unchanged for decades, at around 50-55% overall survival by 5 years. There is, therefore, a need to develop and evaluate new prevention treatments for this condition. It is thought that more effective treatment for oral dysplasia would reduce the incidence of oral cancer.

SAVER is a phase II randomized 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).

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.

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. It is derived from clinical measurement, photographs and punch biopsy tissue comparing baseline to primary endpoint (4 months). Approximately 10 research sites are to be opened to recruitment in the UK.

Previous study hypothesis as of 07/07/2022 to 10/07/2024:
Individuals can develop patches (oral dysplasia) on the lining of the mouth which are at risk of developing into cancer. Standard treatments include surgery or close surveillance, although these treatments are not completely effective, as up to 25% of patients progress to oral cancer even after surgery. Oral cancer treatments can be curative, especially when caught early, but the side effects include damage to speech, swallowing, appearance and reduction in quality of life, which are permanent. Additionally, treatment for oral cancer carries a high economic burden and the World Health Organisation has recommended a shift in policy towards early diagnosis and prevention. Survival rates for oral cancer have remained largely unchanged for decades, at around 50-55% overall survival by 5 years. There is, therefore, a need to develop and evaluate new prevention treatments for this condition. It is thought that more effective treatment for oral dysplasia would reduce the incidence of oral cancer.

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SAVER is a phase II clinical trial with embedded mechanistic and feasibility studies. It is randomized, double blind and placebo controlled with a planned recruitment of 110 patients. The randomisation is in the ratio 2 SV (73 patients) :1 placebo (37 patients). The study

population includes patients with premalignant oral lesions that have a histological diagnosis of oral epithelial dysplasia (OED) and are at high risk (considered to be at least 20% over 5 years of malignant transformation).

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.

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Ethics approval required
Ethics approval required

Ethics approval(s)
approved 22/05/2018, North West - Haydock Research Ethics Committee (3rd Floor - Barlow House, 4 Minshull Street, Manchester, M1 3DZ, United Kingdom; +44 (0)207 104 8012; nrescommittee.northwest-haydock@nhs.net), ref: 18/NW/0180

Study design
Randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Oral epithelial dysplasia

Interventions
Current intervention as of 07/07/2022:
SAVER is a randomised (1 control [no medication]: 2 Sodium Valproate), unblinded, multi-centre placebo-controlled phase II clinical trial investigating the use of sodium valproate in patients with a High Risk Oral Epithelial Dysplasia.

Patients shall be allocated based on a 1:2 allocation ratio with the greater number of patients being allocated to the experimental arm (sodium valproate). The sequences of allocation will be centrally generated by the LCTU study statistician using the Stata package ralloc employing permutated block randomisation with variable block size of 3 and 6. The allocation will be stratified by site and therefore separate randomisation lists will be created for each site. Oral sodium valproate tablets, 1000mg/day (500mg twice daily). Intervention given for 4 months; including ‘step-up’ phase x 2 weeks, at 500mg once daily.

On 26/04/2021 a substantial amendment request was submitted with a trial re-design from double-blinded randomised trial with IMP/Placebo to unblinded randomised trial with IMP /observational control arm (no treatment).

Previous intervention as of 12/07/2021:
SAVER is a randomised (1 Placebo: 2 Sodium Valproate), double-blind, multi-centre placebo-controlled phase II clinical trial investigating the use of sodium valproate in patients with a High Risk Oral Epithelial Dysplasia.

Patients shall be allocated based on a 1:2 allocation ratio with the greater number of patients being allocated to the experimental arm (sodium valproate). The sequences of allocation will be centrally generated by the LCTU study statistician using the Stata package ralloc employing permutated block randomisation with variable block size of 3 and 6. The allocation will be stratified by site and therefore separate randomisation lists will be created for each site. Oral sodium valproate tablets, 1000mg/day (500mg twice daily). Intervention given for 4 months; including 'step-up' phase x 2 weeks, at 500mg once daily.

On 26/04/2021 a substantial amendment request was submitted with a trial re-design from double-blinded randomised trial with IMP/Placebo to unblinded randomised trial with IMP /observational control arm (no treatment).

Previous interventions:
SAVER is a randomised (1 Placebo: 2 Sodium Valproate), double-blind, multi-centre placebo-controlled phase II clinical trial investigating the use of sodium valproate in patients with a High Risk Oral Epithelial Dysplasia.

Patients shall be allocated based on a 1:2 allocation ratio with the greater number of patients being allocated to the experimental arm (sodium valproate). The sequences of allocation will be centrally generated by the LCTU study statistician using the Stata package ralloc employing permutated block randomisation with variable block size of 3 and 6. The allocation will be stratified by site and therefore separate randomisation lists will be created for each site. Oral sodium valproate tablets, 1000mg/day (500mg twice daily). Intervention given for 4 months; including 'step-up' phase x 2 weeks, at 500mg once daily.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Sodium valproate

Primary outcome(s)
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 and it will be derived as a composite score of changes in lesion size, changes in histological grade, and LOH definition at 4 months from the date of commencement of study drug.

Assessment of lesion size
Lesion size will be calculated based on a first assessment of clinical images with lesional size mm2 = pixels of lesional area x 100/(pixels of 1 centimeter unit on the calibration device in the same image)2. Secondary assessment of lesion size will be calculated based on the estimated elliptical area given by the longest length of the lesion and the associated perpendicular width.

Lesion size response will be then measured calculated on a 7 point scale ranging from -3 to 3 based on the change in lesion size between pre and post treatment assessment. Specifically, the relationship between score and outcome is as follows:
• 75% or more decrease = 3
• 50% to 74% decrease = 2
• 25% to 49% decrease = 1
• 0% to 24% decrease or increase = 0
• 25% to 49% increase = -1
• 50% to 74% increase = -2
• 75% or more increase = -3

Assessment of histology response score
Formally, a 0 to 8 grade scale will 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.

Key secondary outcome(s))
Measured at 4 months from the date of commencement of study drug:
1. 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 of SAVER' s protocol
2. Clinical response, as measured by assessment of lesion size as in Section 9.3.1 Section 9.3.1 of SAVER's protocol
3. Histological response, as measured by assessment of histology response score as in Section 9.3.1 Section 9.3.1 of SAVER's protocol
4. LOH Response score, as measured in 9.3.1 Section 9.3.1 of SAVER's protocol
5. WHO grade of OED (or SCC) in entire whole resection specimen (where any oral resection is performed within trial period)
6. Toxicity, measured using CTCAE (Version 4) classifications

Completion date
30/09/2026

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 10/07/2024:
1. Recent (<12 months) histological diagnosis of confirmation of OED according to the World Health Organisation (WHO) criteria (i.e: Patients may be eligible who have a longstanding diagnosis of OED diagnosis but then would need either a recent biopsy (<12 months) or to enter the screening route to randomization)
2. Index lesion* which must be:
2.1. Accessible
2.2. Measurable
2.3. Amenable to clinical photography
2.4. Oral cavity, lip or oropharynx
2.5. Minimum lesion size: 10 mm x 10 mm, or >=100 mm2
(* other 'non-index' lesions in the same patient may be present and do not make the patient ineligible)
3. Treatment plan for either surgical resection, or for surveillance of the lesion by means of clinical and photographic follow-up
4. The index lesion must be considered to be deemed at high risk (i.e. estimated >20% over 5 years) of malignant transformation, i.e.:
4.1. WHO severe OED or
4.2. WHO mild or moderate OED, with at least one additional high-risk feature(s) from the list below:
4.2.1. Non-smoker (less than 100 cigarettes or equivalent over whole lifetime)
4.2.2. Lesion size >200 mm2
4.2.3. Lateral tongue site
4.2.4. Mucosal speckling or heterogeneous appearance
4.2.5. Excised OSCC during previous 5 years (but not within previous 6 months)
5. The patient is fully informed, has received PIS (Patient Information Sheet) & considered during a 'cooling-off' period, is competent to consent, and is able to comply with minimum attendance

requirements
6. Aged ≥55 years

Previous participant inclusion criteria as of 07/07/2022 to 10/07/2024:
1. Recent (<12 months) histological diagnosis of confirmation of OED according to the World Health Organisation (WHO) criteria (i.e: Patients may be eligible who have a longstanding diagnosis of OED diagnosis but then would need either a recent biopsy (<12 months) or to enter the screening route to randomization)
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4.2.2. Lesion size >200 mm2
4.2.3. Lateral tongue site
4.2.4. Mucosal speckling or heterogeneous appearance
4.2.5. Excised OSCC during previous 5 years (but not within previous 6 months)
5. The patient is fully informed, has received PIS (Patient Information Sheet) & considered during a 'cooling-off' period, is competent to consent, and is able to comply with minimum attendance requirements
6. Aged ≥18 years

Previous participant inclusion criteria:
1. Recent (<12 months) histological diagnosis of confirmation of OED according to the World Health Organisation (WHO) criteria (i.e: Patients may be eligible who have a longstanding diagnosis of OED diagnosis but then would need either a recent biopsy (<12 months) or to enter the screening route to randomization)
2. Index lesion* which must be:
2.1. Accessible
2.2. Measurable
2.3. Amenable to clinical photography
2.4. Oral cavity, lip or oropharynx
2.5. Minimum lesion size: 10 mm x 10 mm, or >=100 mm2
(* other 'non-index' lesions in the same patient may be present and do not make the patient ineligible)
3. Treatment plan for either surgical resection, or for surveillance of the lesion by means of clinical and photographic follow-up
4. The index lesion must be considered to be deemed at high risk (i.e. estimated >20% over 5 years) of malignant transformation, i.e.:
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4.2. WHO mild or moderate OED, with at least one additional high-risk feature(s) from the list

below:
4.2.1. Non-smoker (less than 100 cigarettes or equivalent over whole lifetime)
4.2.2. Lesion size >200 mm2
4.2.3. Lateral tongue site
4.2.4. Mucosal speckling or heterogeneous appearance
4.2.5. Excised OSCC during previous 5 years (but not within previous 6 months)
5. The patient is fully informed, has received PIS (Patient Information Sheet) & considered during a 'cooling-off' period, is competent to consent, age >=18, and is able to comply with minimum attendance requirements

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
55 years

Upper age limit
100 years

Sex
All

Total final enrolment
80

Key exclusion criteria
Current participant exclusion criteria as of 10/07/2024:
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. Immunosuppression, 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:
9.1. Acute porphyria
9.2. Known or suspected mitochondrial disorders
9.3. Personal or family history of severe hepatic dysfunction, as defined by Child-Pugh Group C (see appendix 5)
9.4. current hepatic dysfunction (as evidenced by LFTs significantly outwith reference range or prolonged prothrombin time)

9.5. Past history or current pancreatitis
9.6. 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.
9.7. 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)
9.8. 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.
9.9. Patients with known or suspected mitochondrial disease, systemic lupus erythematosus or hyperammonaemia

Previous participant exclusion criteria:
1. Synchronous or metachronous OSCC (i.e. at time of screening or within 6 months)
2. Active malignancy outside head and neck region (with exception of non-melanoma skin cancer)
3. Inflammatory co-existing oral lesions: lichen planus, fungal (candidiasis) oral lesions, scleroderma
4. OSCC susceptible conditions e.g. Fanconi Anaemia, Bloom's syndrome, Ataxia Telangectasia, Li Fraumeni syndrome etc
5. Clinical and/or histopathological diagnosis of oral submucous fibrosis
6. Immunosuppression, however, low dose i.e. < 10mg/day prednisolone, or equivalent steroids, are not considered an exclusion
7. Chronic previous or current use of Sodium Valproate
8. Diagnosed epilepsy that has chronic previous or current use of any antiepileptic therapy
9. Obesity (Body Mass Index >= 30)
10. Known relative or absolute contraindications to Sodium Valproate (as listed in British National Formulary), and specifically:
10.1. Acute porphyria
10.2. Known or suspected mitochondrial disorders
10.3. Personal or family history of severe hepatic dysfunction, current hepatic dysfunction (as evidenced by LFTs outwith reference range and prolonged prothrombin time)
10.4. Past history or current pancreatitis
10.5. Women with childbearing potential (< 2 years post menopause), pregnancy, breastfeeding. (This is iterated in more detail in SOP as per appendix 1)
10.6. Potential drug interactions (particularly antipsychotic and anticonvulsant medications, MAO inhibitors, antidepressants, benzodiazepines), specifically patients taking phenobarbital, primodone, carbopenem antibiotics (imipenem, panipenem, meropenem), cimetidine, erythromycin, lamotrigine, olanzapine, pivmecillinam, sodium oxybate, zidovudine, carbamazepine, phenytoin, rifampicin, salicylates e.g. aspirin
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10.8. Patients with known or suspected mitochondrial disease, systemic lupus erythematosus or hyperammonaemia

Date of first enrolment
15/10/2019

Date of final enrolment
30/11/2024

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Liverpool University Dental Hospital (lead centre)
Department of Oral Medicine
Pembroke Place
Liverpool
England
L3 5PS

Study participating centre
Aintree University Hospital NHS Foundation Trust
Head & Neck Oncology Clinical Trials
Longmoor Lane
Fazakerley
Liverpool
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L9 7AL

Study participating centre
Leeds Dental Institute
Leeds Teaching Hospitals NHS Trust
Oral and Maxillofacial Surgery
Clarendon Way
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LS2 9LU

Study participating centre
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Oral Medicine Unit
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Study participating centre
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Study participating centre
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Bristol
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BS2 8HW

Study participating centre
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Scotland
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Study participating centre
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Foresterhill Road
Aberdeen
Scotland
AB25 2ZN

Sponsor information

Organisation
University of Liverpool

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 14/209/13

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		05/07/2021	07/07/2021	Yes	No
HRA research summary			28/06/2023	No	No
Other publications	Perceptions of chemoprevention among individuals at high risk of oral cancer: qualitative study within the UK-based SAVER trial	17/06/2025	18/06/2025	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes