LISTER

Lugol's Iodine in Surgical Treatment of Epithelial Dysplasia in the ORal Cavity and Oropharynx

A feasibility, multicentre randomised controlled trial assessing the effectiveness of Lugol's Iodine to assist surgical excision of epithelial dysplasia in the oral cavity and oropharynx

PROTOCOL VERSION: 1.2

DATE: 27 FEBRUARY 2017

ISRCTN NUMBER: 11348079
REC NUMBER: 16/LO/0857
FUNDERS: Oracle Cancer Trust and LNWH Charitable Trust

ORACLE cancer trust

London North West Healthcare NHS
NHS Trust

TRIAL SPONSOR
NHS Greater Glasgow and Clyde
Clinical Research and Development Central Office
West Glasgow Ambulatory Care Hospital
Dalnair Street
Glasgow G3 8SW
Tel: 141 232 1818
Emai: Joanne.McGarry@ggc.scot.nhs.uk

Tel:

CHIEF INVESTIGATOR
Professor Jim McCaul
Maxillofacial Department
Queen Elizabeth University Hospital
1345 Govan Rd
Glasgow, G51 4TF
Tel: 0141 201 1100
Email: jim.mccaul@mac.com

Email: jmccaul@nhs.net

TRIAL COORDINATOR
Jacqueline Quantrill
Head and Neck Research
Research & Development

Bradford Institute for Health Research
Bradford Royal Infirmary
Duckworth Lane
Bradford, BD9 6RJ
Email: jaqueline.quantrill@bthft.nhs.uk
Tel: 01274 27 3921

Jacqueline Quantrill
Bradford Institute for Health Research
Bradford Royal Infirmary
Duckworth Lane
Bradford, BD9 6RJ
Email: jaqueline.quantrill@bthft.nhs.uk
Tel: 01274 273921

CONTACT DETAILS

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	**Explanation**
CRF	Case Report Form
CTU	Clinical Trials Unit
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMEC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
LISTER	Lugol's Iodine in Surgical Treatment of Epithelial Dysplasia in the Oral Cavity and Oropharynx
MDT	Multi-Disciplinary Team
REC	Research Ethics Committee
QoL	Quality of Life
R&D	Research and Development
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TSC	Trial Steering Committee

1. BACKGROUND

Oral dysplasia is a relatively common premalignant condition, affecting 2.5 to 5 per 1000 of the population[1]. Patients with mucosal abnormality detected in primary care are referred under the two week wait system for assessment in secondary care. Clinically detected red (erythroplakia), white (leukoplakia) and mixed (erythroleukoplakia) areas of mucosal change, persisting after causative factors (such as use of tobacco) have been eliminated, will be subject to incisional biopsy[2]. In some of these cases dysplasia will be detected. The grade of dysplasia is determined by the degree of cellular abnormality above the epithelial basement membrane, as defined by the World Health Organisation (WHO) [3-5].

Epithelial dysplasia is regarded as one of the most significant indicators of malignant potential. Oral dysplasia carries a significant rate of transformation to cancer. A meta-analysis of 14 studies involving 992 patients[1] showed a mean transformation rate of 12.3%, with a wide variation between studies (from 0% to 36.4%), increasing considerably for high grade dysplasia (24.1%). Liu et al[6] reported that high grade dysplasia had a considerable higher incidence of malignant change (5-year oral-cancer free survival 59%) than low grade dysplasia (90.5%). A recent study following prospectively during 10 years the outcome of 100 patients with dysplastic lesions excised by laser surgery reported a 7% rate of malignant transformation[7].

Complete excision of high risk lesions is recommended[8, 9,10] and excision of such areas is associated with a reduction in malignant transformation (5.4% after surgery vs 14.6% with no surgery)[1]. However, reported cure rates after laser surgery vary between 33.9% and 82%, and recurrence rates between 7.7% and 66%[11]. Difficulty in assessing extent of the dysplastic lesion at time of surgical excision contributes to persistence of dysplasia involved margins and therefore persistence of residual dysplastic mucosa.

The full extent of pre-malignant disease is difficult to distinguish clinically but visualisation with Lugol's iodine is effective in identifying pre-cancerous lesions at other histologically similar body sites[12-14]. Lugol's iodine stains glycogen in normal squamous epithelium to a chocolate brown colour. Where mucosal squamous epithelium is dysplastic, loss of differentiation and deregulated cytosol glycolysis produced by the Warburg effect[15], mean

that glycogen is no longer stored. The dysplastic epithelium stains saffron yellow, and can therefore be seen by the naked eye at time of resection.

This technique in the context of invasive cancer resection is the subject of a CRUK funded randomised clinical trial, the LIHNCS trial (CRUK/10/011[16]). LIHNCS assesses the use of staining with Lugol's iodine in the context of diagnosed invasive SCC of the oral cavity and oropharynx. LISTER will follow on from this in the context of early detection and prevention of malignant transformation. Evidence from quality follow-up data for oral dysplasia is limited[1,7,17]. There is a lack of randomised clinical trials providing evidence-based recommendations for specific surgical interventions of dysplastic oral lesions[7,18], nor previous studies which properly evaluate this visualisation technique in this patient population for this disease site.

The study will run comfortably alongside current surgical practice, aiming to improve accuracy of treatment both by removing all dysplastic tissue while minimising removal of normal tissue.

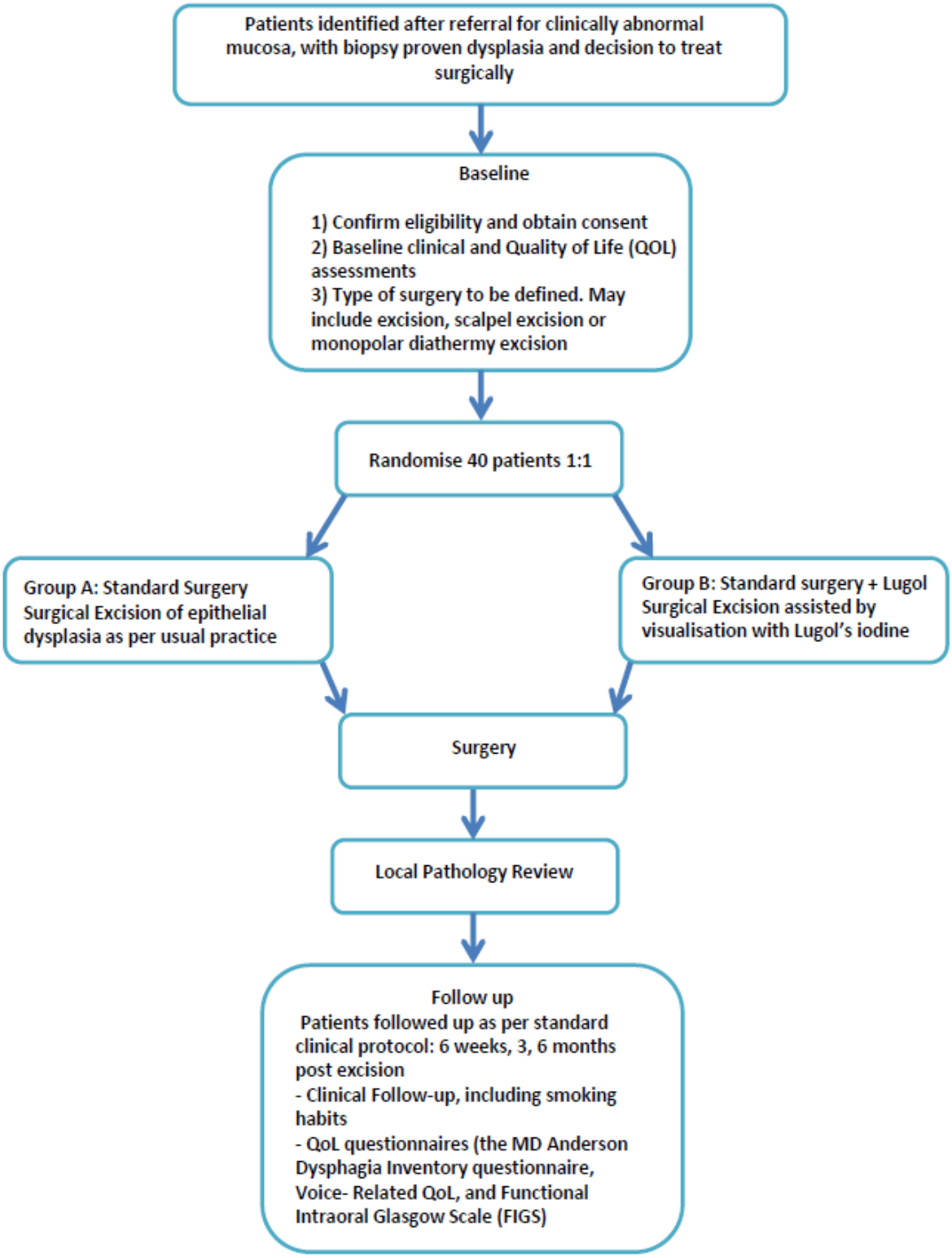
2. TRIAL DESIGN

2.1 Trial Summary

Epithelial dysplasia is regarded as one of the most significant indicators of malignant potential. Oral dysplasia carries a significant rate of transformation to cancer. This trial therefore aims to reduce the presence of these precancerous cells, through the use of Lugol's Iodine.

During surgery and prior to resection, Lugol's Iodine is applied to the dysplastic patch and the surrounding area. The dysplastic cells should not take up the stain, therefore leaving a pale area to be resected. This technique should allow for improved removal of moderate and severe dysplasia.

FIGURE 1 TRIAL FLOW DIAGRAM



2.2 Objectives

The primary objective is to determine the acceptability of the research to patients.

Primary Outcome Measure

- Acceptability of the research to patients

Secondary Outcome Measures

- Incidence of dysplasia at resection margins
- Patient reported quality of life
- Transformation to SCC at 6 weeks, 3 and 6 months post-surgery
- Presence of invasive carcinoma detected after excision
- Surface area of tissue excised
- Acceptability and safety of the technique to surgeons

2.3 Power and Sample Size

For the feasibility stage of the research the target sample size is 40 patients, with an estimated recruitment rate of 8-10 patients per site per year over a one year recruitment period.

If the primary objective is met LISTER will progress to a larger scale trial with a sample size of 388. The following statistical computation regarding sample size has been calculated;

In a recent cohort of 100 patients presenting dysplastic lesions in the oral cavity and undergoing excision by laser surgery, a 52% rate of positive margins (presence of dysplasia or carcinoma in situ in the excision margins) was reported. Following 2013 surgical records from Bradford Teaching Hospitals NHS Foundation Trust, such rate would range from 37.8% to 75% (different surgeons, personal communication). Assuming that the rate of positive margins is 50% in the control group, we would need 388 patients (194 per group) to be able

to detect at least a 1/3 reduction in the rate of positive margins (33.3% relative reduction, or equivalently, from 50% in the control group to 33.4% in the Lugol's group). We have explored the impact that deviations from such assumptions may have on the power of the study. In the case that the proportion of patients with positive margins after surgery is higher than anticipated (e.g. >50%), a sample size of 388 patients would allow us to detect equivalent 1/3 relative reductions with >90% power. In the case that the proportion of patients with positive margins after surgery is lower than anticipated (e.g. <50%), the power to detect 50% relative reductions equivalent relative reductions of 1/3 would be of >80%, >70% or 57% power (for control rates of 45%, 40% or 30%, respectively). In all the previous scenarios, we would have more than 90% power to detect 50% relative reductions.

2.4 Eligibility Criteria

Patients are eligible to be included in the trial if they meet the following criteria:

2.4.1 Inclusion criteria

- Provision of written informed consent.
- Age≥ 18 years old.
- Epithelial dysplasia of the oral cavity or oropharynx, undergoing primary surgical excision under general anaesthesia.

2.4.2 Exclusion criteria

- Previous surgery or radiotherapy for head and neck cancer.
- Allergy to iodine
- Previous diagnosis of head & Neck SCC in the past 5 years or active malignancy within 2 years of randomisation (except basal cell carcinoma or carcinoma of the cervix in-situ).

Informed consent

The Investigator will discuss the trial during the clinic appointment when treatment options are discussed. Patients will be given an appropriate length of time before their treatment starts to decide if they would like to participate or not. Some patients may not require 24 hours; however others will wish to have longer. This will be discussed with the patient and assessed by the clinical and research team. Signed and dated informed consent must be obtained before conducting any procedure specifically for the trial, by someone trained and delegated to do so.

2.5 Recruitment and Randomisation

For each patient considered suitable for inclusion in the LISTER trial, the following events will take place:

1. Clinical decision to treat with primary surgery and for LISTER trial consideration.

2. If the patient is deemed eligible as per trial protocol, the research team are informed of the date the patient is coming to clinic to discuss treatment.

3. Clinician discusses diagnosis with patient and carers and discusses treatment options including the need for primary surgery. If the patient agrees to this treatment, the clinician then mentions that there is a study and introduces the research nurse/coordinator.

4. The research nurse/coordinator discusses the trial in detail with the patient and their carers and answers queries. She/he presents the patient information leaflets and offers the trial to the patient.

5. The patient is offered ample time to think about the trial (where possible, not less than 24 hours) and a further appointment can be arranged for the patient and carers to ask further questions or to meet their clinicians if they wish.

6. If the patient wishes to proceed, written patient consent is obtained. A sticker is placed in the notes, confirming that the patient is eligible.

7. The patient is asked to complete the baseline QoL questionnaire.

8. The Eligibility and Randomisation CRF is completed and signed by the investigator prior to attempting to randomise a patient.

9. Once the Eligibility and Randomisation CRF is complete, the clinician or research nurse calls the randomising office.

11. The allocated treatment and patient trial number will be told over the phone.

12. The GP letter should be completed and sent by clinician or research nurse, unless patient has declined this.

13. If the MDT or clinician does not wish to enter an eligible patient into the trial or if a patient refuses or is deemed non-eligible, please complete the non-randomisation log.

Randomisation

Tel: 01274 27 3921 or Email: jacqueline.quantrill@bthft.nhs.uk
Once consent is complete, randomisation can be done at anytime prior to date of surgery. Please let the trial centre know in as much time as possible that you will be randomising a patient.

2.6 Trial Intervention and Control

Patients in the intervention arm will have the dysplastic area stained with Lugol's Iodine, those in the control arm will not. This means that for patients in the treatment arm, during surgery and prior to resection, Lugol's Iodine is applied to the dysplasia and the surrounding area. The dysplastic cells should not take up the stain, therefore leaving a pale area to be resected. All other intraoperative procedures will be the same between trial and control arms. The intraoperative procedures SOP must be followed for all trial patients and will be supplied separately to trial sites. This covers application of Lugol's Iodine and preparation of resected tumour for histopathology.

2.7 Blinding

Patients will be blinded to their randomisation. The Investigator, surgeons and health care professionals will not be blinded; however they will not divulge the randomisation to the

patient. Pathologists will be blinded as the samples do not retain the iodine colour, so this stops bias in reporting of the primary outcome.

The randomisation arm will be recorded on the Eligibility and Randomisation CRF, and confirmed on the Surgery CRF. However the Chief Investigator must be made aware of any unblinding to the patient and this must be documented in the patient's medical notes.

Treatment codes will not be broken for the planned analysis of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

2.8 Withdrawals and Transfers

Patients should be encouraged to remain within the trial. However, patients have the right to withdraw from the study at any time. Every effort should be made to identify the following:

- Reason for withdrawal
- Whether the patient still gives consent to collect QoL information

  Or…

- Whether the patient still gives consent to collect follow-up information on survival only

  Or…

- Whether patient withdraws completely from the trial, and does not want any further data to be collected on them.

If a patient chooses to completely withdraw, this must be noted in the patient's medical notes. Any information already collected should be kept, but no further data should be collected about the patient. The above information must be recorded on the Withdrawal/Transfer Form and the LISTER trial office must be informed as soon as possible. Subjects may be withdrawn from the trial at the discretion of the Investigator and/or Trial Steering Committee due to safety concerns. Patients, who change their mind about

withdrawal and wish to re-join the study, can do so at any time. They should be re-consented, and follow-up data should be collected only from that point onwards.

Patients moving out of the area

Every effort should be made to transfer the follow-up of patients moving away from the area to another participating trial centre, which will take over the responsibility for follow-up. The Withdrawal/Transfer Form should be completed and sent to the Trial Office. Close co-ordination with the LISTER trial office is essential. A copy of the patient's CRFs must be sent to the new trial centre.

3. METHODS AND ASSESSMENTS

3.1 Schedule of Investigation and Data Collection

Patients will be recruited over a 1 year period and followed up for a minimum of six months. The LISTER intervention is carried out in theatre during surgery; there is no further intervention from that point. Patients will be assessed at 6 weeks, 3 months and 6 months post excision. At each time point a data capture form will be completed by the clinician/research nurse. Patients will be followed up according to standard clinical practice post excision for oral cavity and oropharyngeal dysplasia. The presence of clinically abnormal mucosa will be monitored at each visit. If present, this would trigger (incisional) biopsy in order to determine histology of the suspicious lesion as per standard practice. The details and outcome of such investigations (confirmed dysplasia, SCC, other) will be recorded.

3.2 Quality of Life

The patient will be requested to complete the following quality of life questionnaires measuring speech, chew, swallow and/or pain assessments: MD Anderson Dysphagia Inventory, Numeric Pain Rating Scale (0-10), Voice-Related Quality of life V-RQOL and the Functional Intraoral Glasgow Score FIGS.

The QoL booklet will be distributed to sites with the CRFs. The Researcher will print off the booklet and then patients are asked to complete them in clinic. They may ask their relatives

or the clinic nurses or researchers to help them complete the questionnaires. Patients should attempt to answer all questions, but those questions that the patient does not want to answer can be left empty.

Researchers or trial nurses should ensure that at each time point:

- all the questionnaires have been completed
- patient identifier is written on the booklet
- date of completion is written on booklet

Questionnaire booklets will be handed out and completed at the follow-up visits. Patients should be asked to arrive 30 minutes before their clinic appointment to allow time for completion of the questionnaires. Patients who did not attend their appointment should be contacted. The questionnaire booklet can be completed over the telephone or sent to them by post for completion. If the patient does not return the questionnaire, they should be contacted once by letter and then one final time by phone as a reminder.

Table 1. Schedule of Investigations

Assessments	Prior to Randomisation	Baseline	Post-Surgery	6 week Follow-up	3 month Follow-up	6 month Follow-up
Review Inclusion/ Exclusion criteria	x					
Written Informed consent	x					
Clinical Examination		x		x	x	x
Tobacco and alcohol use		x		x	x	x
QoL Questionnaires		x		x	x	x
ECOG status		x		x	x	x
Surgery and Surgical complications form			x			
Histopathology	x[a]					
Complications		x[b]	x[b]	x[b]	x[b]	x[b]

a. to confirm initial dysplasia diagnosis
b. to be reported as appropriate throughout trial

4. ADVERSE EVENT REPORTING

This technique is widely used at other body sites and there are some very rare reports of adverse tissue reactions. These surface changes are reported to have resolved within one week. We therefore anticipate that the risk of any adverse effect is minimal.

Due to this being a surgical trial, not a CTIMP, and the one trial intervention completed during surgery is transient in nature, the following details relate to reporting complications and SAEs. Complications will be reported at the following time points:

- Intraoperatively, during surgery
- Throughout the initial inpatient stay
- Each follow-up time point

4.1 Reporting Serious Adverse Events

A complication is deemed **serious** if it meets one of the following criteria:
Death

- Life threatening
- Hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect
- Other medically significant reason

However:
Complications that are considered serious are **ONLY** reported as SAEs for the duration of the patients initial inpatient stay; from time of surgery, up until first discharged.

If during that time an SAE is thought to be related to being involved in the trial and that it is unexpected, then the Trial Office will report it to the REC.

The Principal Investigator in each centre must report any SAEs to the Trial Co-ordinator within 24 hours of them becoming aware of it. The SAE form should be completed and faxed to the Trial Co-ordinator who will then liaise with the Investigator to compile all the necessary information. The Trial Office is responsible for reporting SAEs to the Sponsor and REC within the required timelines.

4.2 End of Trial

The trial will end when all recruited patients have undergone local pathology review and completed six months follow-up.
The primary outcome measure will be answered at the end of the recruitment period. The secondary outcome measures will be assessed during routine follow up of the patients in both groups.

The trial will be stopped prematurely if:

- Mandated by the REC
- Following recommendations from the Trial Steering Committee (TSC)
- Funding for the trial ceases
- The REC and Sponsor will be notified in writing if the trial has been concluded or terminated early

5. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with the 1998 Data Protection Act. All patients will be identified by a unique trial number, along with their initials and date of birth.

5.1 Data Collection and Management

Researchers at each individual site will complete the CRFs. Electronic pdf versions of all CRFs will be sent to the main site contact following site initiation. Each form will then be printed by the site as and when needed for each recruited patient. The original will be sent to the Trial Co-ordinator, and a photocopy is to be kept at the site. The Trial Co-ordinator will create and chase data queries and chase any missing/outstanding CRFs. A copy of the patient's consent form, with trial number completed must be sent by fax, email or post to the Trial Co-ordinator as soon as possible following randomisation.

5.2 Data Storage

All essential documentation and trial records will be stored at NHS Greater Glasgow and Clyde Bradford Teaching Hospitals NHS Foundation Trust in accordance with the applicable regulatory requirements and where access to stored information will be restricted to authorised personnel.

5.3 Archiving

Essential documentation will be archived at Queen Elizabeth University Hospital and at the investigator sites. Trial documentation at investigator sites should be archived for at least five years after 'last patient last visit'.

6. STATISTICAL ANALYSIS

Analyses will be according the intention-to-treat principle. Presence of dysplasia at excision margins will be summarized with frequencies and group percentages, and treatment arms will be compared by a chi-square test (or Fisher's exact test as appropriate). Unadjusted odds ratios (OR) estimating treatment effects and their 95% CI will be produced. Extended logistic regression models will be considered to adjust for stratification factors (site and subsite of excision and surgeon) and other possible prognostic factors, such as size of the

lesion or dysplasia grade. Surgeon will be included as a random effect in the model. Adjusted OR and 95%CI will be derived from these models.

Similar statistical analysis methods will be employed to analyse other categorical secondary endpoints. Continuous secondary endpoints will be summarised (median, IQR, range) by treatment group and at each time point (for QoL measurements), and groups compared statistically by parametric or non-parametric tests as appropriate. Analysis to account for the longitudinal nature of the data may be used. A planned exploratory subgroup analysis will be performed to investigate the treatment effect in each site and/or sub site**.**

7. TRIAL ORGANISATION AND OVERSIGHT

This trial will be carried out in accordance with the ICH GCP Guidelines, and adheres to the Research Governance Framework for Health and Social Care (2nd edition, DOH 2005)12. This trial does not fall under the remit of the Medicines for Human Use (Clinical Trial) Regulations 2004, as it is not a CTIMP.

7.1 Ethical Conduct of the Trial

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the subsequent amendments. The Declaration of Helsinki can be found on the World Medical Association website http://www.wma.net.

This protocol has been REC approved. Before entering patients into the study, the responsible investigator at each site must ensure that the protocol has the approval of the relevant NHS Trust. The LISTER Trial Office will send an annual trial update report to the REC which will be forwarded to each participating centre, together with details of their individual recruitment.

Informed consent

It is the responsibility of the Investigator or their delegated staff to obtain written informed consent in compliance with national requirements, from each subject prior to them entering the trial. The Patient Information Sheet must be printed on local hospital headed paper before being distributed to patients.

Patient identification data (patient initials and NHS number) will be recorded on screening logs to assist with long-term follow-up. Before entering subjects into the study, written approvals from each site's Trust R&D must be submitted to the Trials Office and a site activation letter must have been received at site.

Protocol amendments

Sites will be notified of any amendments made to the protocol, which should then be submitted to their R&D for approval. Any changes should only be implemented following approval. However, this does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interests of individual patients.

7.2 Sponsor

NHS Greater Glasgow and Clyde will act as sponsor for this trial.

7.3 Financial Support

The trial is funded jointly by Oracle Cancer Trust and London North West Hospitals Charitable Trust.

7.4 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk.

The NHS indemnity scheme will also cover for any harm caused to patients by the design of the research protocol.

7.5 Trial Timetable and Milestones

Planned start date: 01/05/2016
First patient recruited: 01/06/2016
Planned end of recruitment: 01/12/2018
Planned end date with follow-up: 01/06/2019

7.6 Administration

The trial is run from the Trial Office based at Bradford Institute for Health Research. The clinical aspects of the trial are the responsibility of the Chief Investigator, Professor James McCaul. The clinical care of the patients is the responsibility of the treating clinician at the individual sites.

A Trial Master File will be set up and held securely at the Trial office, with each site responsible for the set-up and for maintenance of their own site file.

8. MONITORING

Trial Steering Committee

The trial will be guided by a group of respected and experienced personnel and trialists as well as a 'lay' representative. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

9. DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the TSC before submission for publication, on behalf of the collaboration.

The success of the trial depends on the collaboration of doctors, nurses and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

The results will be published in the name of the LISTER Trial in a peer reviewed journal on behalf of all collaborators.

Subjects will be informed of the results through feedback at routine outpatient clinic appointments.

10. REFERENCES

1. Mehanna, H.M., T. Rattay, J. Smith, and C.C. McConkey, Treatment and follow-up of oral dysplasia - a systematic review and meta-analysis. Head & neck, 2009. **31**(12): p. 1600-9.
2. Warnakulasuriya, S., N.W. Johnson, and I. van der Waal, Nomenclature and classification of potentially malignant disorders of the oral mucosa. Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology, 2007. **36**(10): p. 575-80.
3. Barnes, L., J.W. Eveson, P. Reichart, and D. Sidransky, Chapter 4 Tumours of the oral cavity and oropharynx., in World Health Organisation Classification of Tumours. Pathology and genetics of head and neck tumours. 2005, Lyon IARC Press 2005.
4. Kujan, O., R.J. Oliver, A. Khattab, S.A. Roberts, N. Thakker, and P. Sloan, Evaluation of a new binary system of grading oral epithelial dysplasia for prediction of malignant transformation. Oral oncology, 2006. **42**(10): p. 987-93.
5. Pindborg, J.J., P.A. Reichart, C.J. Smith, and I. van der Waal, Histological typing of cancer and precancer of the oral mucosa - 2nd Edition. 1997: World Health Organisation WHO - Springer.
6. Liu, W., L.J. Shi, L. Wu, J.Q. Feng, X. Yang, J. Li, Z.T. Zhou, and C.P. Zhang, Oral cancer development in patients with leukoplakia--clinicopathological factors affecting outcome. PloS one, 2012. **7**(4): p. e34773.
7. Diajil, A., C.M. Robinson, P. Sloan, and P.J. Thomson, Clinical outcome following oral potentially malignant disorder treatment: a 100 patient cohort study. International journal of dentistry, 2013. **2013**: p. 809248.
8. Goodson, M.L. and P.J. Thomson, Management of oral carcinoma: benefits of early precancerous intervention. The British journal of oral & maxillofacial surgery, 2011. **49**(2): p. 88-91.
9. van der Waal, I., Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. Oral oncology, 2009. **45**(4-5): p. 317-23.

10. Kumar, A., L. Cascarini, J.A. McCaul, C.J. Kerawala, D. Coombes, D. Godden, and P.A. Brennan, How should we manage oral leukoplakia? The British journal of oral & maxillofacial surgery, 2013. **51**(5): p. 377-83.
11. Lim, B., A. Smith, and A. Chandu, Treatment of oral leukoplakia with carbon dioxide and potassium-titanyl-phosphate lasers: a comparison. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons, 2010. **68**(3): p. 597-601.
12. Wang, K.K., Detection and staging of esophageal cancers. Current opinion in gastroenterology, 2004. **20**(4): p. 381-5.
13. Inoue, H., J.F. Rey, and C. Lightdale, Lugol chromoendoscopy for esophageal squamous cell cancer. Endoscopy, 2001. **33**(1): p. 75-9.
14. Dawsey, S.M., D.E. Fleischer, G.Q. Wang, B. Zhou, J.A. Kidwell, N. Lu, K.J. Lewin, M.J. Roth, T.L. Tio, and P.R. Taylor, Mucosal iodine staining improves endoscopic visualization of squamous dysplasia and squamous cell carcinoma of the esophagus in Linxian, China. Cancer, 1998. **83**(2): p. 220-31.
15. Vander Heiden, M.G., L.C. Cantley, and C.B. Thompson, Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science, 2009. **324**(5930): p. 1029-33.
16. McCaul, J.A., J.A. Cymerman, S. Hislop, C. McConkey, J. McMahon, H. Mehanna, R. Shaw, D.N. Sutton, and J. Dunn, LIHNCS - Lugol's iodine in head and neck cancer surgery: a multicentre, randomised controlled trial assessing the effectiveness of Lugol's iodine to assist excision of moderate dysplasia, severe dysplasia and carcinoma in situ at mucosal resection margins of oral and oropharyngeal squamous cell carcinoma: study protocol for a randomised controlled trial. Trials, 2013. **14**: p. 310.
17. Smith, J., T. Rattay, C. McConkey, T. Helliwell, and H. Mehanna, Biomarkers in dysplasia of the oral cavity: a systematic review. Oral oncology, 2009. **45**(8): p. 647-53.
18. Brennan, M., C.A. Migliorati, P.B. Lockhart, D. Wray, I. Al-Hashimi, T. Axell, A.J. Bruce, W. Carpenter, E. Eisenberg, J.B. Epstein, P. Holmstrup, M. Jontell, R. Nair, H. Sasser, M. Schifter, B. Silverman, K. Thongprasom, M. Thornhill, S. Warnakulasuriya, and I. van der Waal, Management of oral epithelial dysplasia: a review. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics, 2007. **103 Suppl**: p. S19 e1-12.