Study Protocol for:

Evaluating Gastro-oesophageal Reflux after Palliative Stenting for Malignant Distal Oesophageal Obstruction using Anti-Reflux Stents: a Randomised Controlled Trial

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Evaluating Gastro-oesophageal Reflux after Palliative Stenting for Malignant Distal Oesophageal Obstruction using Anti-Reflux Stents: a Randomised Controlled Trial

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BACKGROUND

Oesophageal cancer is an aggressive condition, resulting in the vast majority of patients having evidence of locally invasive, irresectable disease or distant metastases at the time of presentation[1]. Overall survival remains poor. Management in the South African setting is plagued by late presentation of these patients[2], with less than 5% being eligible for curative treatment [3,4] and median survival from the time of diagnosis being only 15 weeks[4], while those who present with complete obstruction having a median survival of only 75 days (10.7 weeks)[5]. Treatment of these patients in the South African setting remains predominantly palliative. The most common and debilitating symptom of advanced oesophageal malignancy is progressive dysphagia[1], which can be addressed by the endoscopic placement of self-expanding metal stents. The major drawback of stenting tumours in the lower oesophagus or oesophagogastric junction (OGJ), is the associated gastro-oesophageal reflux (GOR) resulting from the stent crossing the lower oesophageal sphincter and essentially negating the native anti-reflux mechanism. Significant reflux is the most common complaint worsening quality of life after stent placement in these patients and can be as high as 100% in some series[6]. Prescribing routine proton pump inhibitors (PPIs) or placing stents with built-in anti-reflux mechanisms are methods aimed at reducing this symptomatic reflux [1].

Diagnosis of GOR in general remains a challenge and numerous diagnostic tests are available. As no specific validation has been done for GOR assessment after placement of oesophageal stents, data on diagnostic techniques of GOR are taken from the primary health care setting or from studies looking at patients who are being considered for, or who have had, anti-reflux surgery. International guidelines, such as the American College of Gastroenterology[7], propose that typical symptoms of GOR confirm a presumptive diagnosis and should prompt empiric medical management (usually with PPIs). Further special investigations to confirm GOR include upper gastrointestinal endoscopy and ambulatory pH monitoring. Barium radiography and oesophageal manometry are not typically recommended as part of the diagnostic work-up[7].

However, all of these tests have drawbacks. Accuracy of diagnosis using only patient-reported symptomatology is non-invasive and with the addition of validated questionnaires[8], reasonably accurate, but it remains subjective and may not differentiate pathological reflux from functional dyspepsia. Endoscopy may reveal visual evidence of GOR, such as reflux oesophagitis or Barrett's oesophagus, which unequivocally prove the presence of GOR[7]. However, non-erosive reflux disease, which is the most common form of GOR, may show no visible abnormalities on endoscopy[7]. Twenty-four-hour pH studies give an objective measure of acid content in the oesophagus and allow for matching of patient reported symptoms to reflux events. Accuracy is further increased when impedance is added to the pH-metry as this will diagnose non-acid reflux which is missed when pH-metry is used alone[7]. Despite reported high accuracy rates using pH-impedance studies in patients with erosive reflux disease, the accuracy rates drop significantly in patients with endoscopy-negative GOR[7]. The necessity of a trans-nasal catheter for a period of 24 hours, also makes this test more invasive than other modalities.

Although not included in these guidelines, oesophageal scintigraphy is a diagnostic modality available to objectively confirm and quantify gastric contents refluxing up the oesophagus. It has the advantage of assessing oesophageal transit, GOR and gastric emptying[9]. Scintigraphy has also been shown to be an accurate modality to confirm the presence of laryngopharyngeal reflux or gastric content aspiration into the lungs[10]. Although not commonly described in the literature on the diagnosis of GOR in adults, its use is much more common in the paediatric setting. International paediatric guidelines[11] describe the use of oesophageal scintigraphy in diagnosing GOR, although there is insufficient evidence to

support the routine use of scintigraphy in making the diagnosis. Scintigraphy remains the standard technique for assessing gastric emptying, which if delayed, may be an important underlying cause for GOR[11]. Despite the guidelines, the use of scintigraphy to diagnose GOR is considered very useful in paediatrics [12] and is commonly used in some institutions. The Red Cross War Memorial Children's Hospital routinely use oesophageal scintigraphy, the so-called "milk scan", to work up paediatric patients with suspected severe reflux who might require anti-reflux surgery[13]. The role of scintigraphy in the diagnosis of GOR in the adult setting remains undefined.

Theoretically, oesophageal stents containing an anti-reflux valve should provide a physical barrier to prevent gastric content (which may be acidic or non-acidic) refluxing into the oesophagus, but whether this results in decreased rates of GOR in reality is somewhat controversial. To date, a number of trials have compared a range of anti-reflux oesophageal stents to conventional oesophageal stents and although there have been some conflicting results, a systematic review and meta-analysis in 2019[1] concludes that GOR is not significantly reduced by the use of anti-reflux stents. However, there are a number of factors that must be mentioned before this conclusion can be applied to dictate clinical practice. Firstly, the included trials all have reasonably small participant numbers, with 65 patients being the highest number of patients enrolled in any of these trials [14]. In fact, the authors conclude that the meta-analysis is underpowered. Furthermore, the type of anti-reflux stent used varies with almost every trial and may well influence efficacy of reducing GOR. Anti-reflux medical therapy such as the use of proton pump inhibitors (PPIs) also varied greatly amongst the studies. Some prescribed PPIs only to the conventional stent group [15], others did not use PPIs in either group [16], while the rest did not mention whether PPIs were routinely given or not. This could possibly influence symptomatic reflux and act as a significant confounding factor.

The measurement of GOR in the trials assessed in this meta-analysis shows significant heterogeneity, with some studies using patient questionnaires (some of these assess quality of life in general and do not specifically focus on reflux symptoms), others use contrast oesophagography [15,17] or functional 24-hour pH monitoring [16,18,19]. These additional factors make the results of this underpowered meta-analysis difficult to interpret.

Since then, a further randomised controlled trial (RCT) was conducted by Dua *et al* [6]. This included a total of 60 patients, comparing a novel tricuspid-shaped valve anti-reflux stent (30 patients) to conventional stenting (30 patients). Importantly, this trial was a non-inferiority trial to assess safety and efficacy at improving dysphagia for the new stent. Assessment of GOR was a secondary outcome and although reflux rates favoured the new anti-reflux stent, this did not reach statistical significance. The current level I and II evidence on reducing GOR with anti-reflux stents is thus not definitive and leaves the topic unresolved.

What is less controversial, are the data on safety and efficacy at dysphagia improvement using anti-reflux stents. The pooled data of the meta-analysis show that there are no significant differences in stent-related complications between the anti-reflux stents and conventional stents, specifically stent migration, bleeding and stent occlusion [1]. Improvement in dysphagia was similar between the two stents, actually slightly favouring the anti-reflux stent group, but not reaching statistical significance. Another systematic review and meta-analysis focusing specifically on oesophageal stents placed for malignant obstruction, showed that treatment-related deaths were actually reduced when anti-reflux stents were used [20]. Thus, using anti-reflux oesophageal stents does not raise any additional safety concerns when compared to conventional stents.

While research in high income countries is focused on the management of early oesophageal malignancies, this is not appropriate in the South African setting where the vast majority of patients are irresectable at initial presentation. Local research is significantly limited[21] and there is a paucity of data from South Africa, and Africa as a whole, as regards the palliative management of malignant oesophageal dysphagia. Specific evidence on the use of anti-reflux stents is absent. Further research is thus invaluable in assessing if the palliative care of these patients can be improved by using anti-reflux stents.

This prospective randomised controlled trial aims to compare the incidence of symptomatic volume GOR after the use of anti-reflux oesophageal covered metal stents versus conventional oesophageal covered metal stents for lower oesophageal malignant strictures in a South African tertiary referral centre with a high rate of palliative stenting for advanced oesophageal carcinoma.

AIM AND OBJECTIVES

Aim

This prospective randomised controlled trial will aim to compare symptomatic volume GOR, when using anti-reflux oesophageal stents versus conventional oesophageal stents, in the palliative management of patients with lower oesophageal or OGJ carcinomas.

Primary Objective/Hypothesis to be Tested

The primary objectives of this trial will be to compare rates of self-reported, symptomatic volume GOR and objectively measured rates of volume GOR using scintigraphy, between the two study groups. This will be a superiority trial, with the hypothesis being that palliative oesophageal anti-reflux self-expanding fully covered metal stents significantly reduce volume GOR compared to conventional oesophageal self-expanding fully covered metal stents.

Secondary Objectives

Secondary objectives will be to compare outcomes, including rates of dysphagia, cough, pain, stent-related complications, subsequent complications and patient survival at the end of the study period. A further objective will be to compare the self-reported GOR questionnaire (GerdQ) outcomes to the objectively measured oesophageal scintigraphy measurements.

METHODS

Trial Design

This study will be a prospective randomised controlled trial comparing anti-reflux oesophageal stents to conventional oesophageal stents. Randomisation to an anti-reflux stent versus a conventional stent will be done prior to stent placement and the patient will remain blinded to the type of stent placed. Although the authors will not be blinded to the stent type, as the stents are easily distinguished from each other at the time of endoscopy, the Clinical Coordinator who will be doing the follow-up will be blinded to this. This study will be performed following the CONSORT 2010 checklist of information for randomised trials [22].

Once the study is approved by the University of Cape Town's Human Research Ethics Committee, approval for the study will also be obtained from Groote Schuur Hospital. The trial will then be registered with the South African National Clinical Trials Register (SANCTR) and at clinicaltrials.gov. Both stents being compared in this trial are already approved by the South African Health Products

Regulatory Authority (SAHPRA), and as they form part of standard of care, application to SAHPRA will not be necessary.

Participants
Eligibility criteria for trial participants:

Inclusion Criteria (all criteria must be met):

- Adult patients - 18 years of age or older
- Informed consent obtained from the patient after oral and written explanation of the trial
- Histologically confirmed malignancy of the distal oesophagus or OGJ
- Obstructive or irresectable malignancy due to metastases, local tumour infiltration or poor performance status
- Once deployed, the distal end of the stent must have crossed the OGJ junction and be lying within the proximal stomach

Exclusion Criteria:

- Patient declining or unable to give informed consent, including inability to speak or understand either English, Afrikaans or isiXhosa.
- Patient unable to comply with the follow-up protocol of the trial (e.g. does not have a contactable telephone number)
- Oesophageal cancers selected for curative treatment or irresectable oesophageal cancers selected for palliative chemoradiation, but not requiring oesophageal stenting
- Benign oesophageal pathology or extrinsic compression of the oesophagus from another cause
- Patients with oesophageal cancers where the stent does not cross the OGJ
- Pregnant patients
- Patient performance status precluding any intervention or sedation

Setting and Location of Trial
This trial will take place at the Upper Gastrointestinal Surgery Unit at Groote Schuur Hospital (GSH). All stent insertions for the trial will be performed by either of the two full-time consultants working in the Upper Gastrointestinal Surgery Unit at GSH. Palliative oesophageal stenting is performed in the endoscopy suite in E23 under conscious sedation. After appropriate post-procedural observation in the unit, the patient will be admitted to the hospital for overnight observation and if deemed well enough, will be discharged home the following day after the scintigraphy.

Interventions
Patients considered eligible for the trial will be enrolled after obtaining informed consent. Oesophageal stenting will be performed according to standard practices at the GSH endoscopy suite using video endoscopy (standard gastroscope) and fluoroscopy. Patients will be appropriately sedated for the procedure, provided with supplemental oxygen and a diagnostic upper gastrointestinal endoscopy will then be performed to confirm the site and length of the histologically confirmed oesophageal cancer. Randomisation will then occur only if stenting is required which will result in OGJ overlap. Regardless of which type of stent the patient receives, all enrolled participants will be prescribed a twice daily dose of a proton pump inhibitor post the procedure, which is continued indefinitely as per the current standard of care at GSH.

Randomisation will be done using opaque, sealed envelopes with computer-generated random numbers in blocks of 20 (10:10). Patients will be randomised to either receive a conventional oesophageal stent or an anti-reflux oesophageal stent. Other than the anti-reflux mechanism, all other parameters of the two stents will be the same – both stents will be fully covered Nitinol self-expanding metal stents designed for deployment in the oesophagus (conventional stent: Taewoong Niti-S Esophageal Covered Stent, distributor: First Medical Company [Global Medical Device Nomenclature Code 61751] and anti-reflux stent: Taewoong Niti-S Esophageal Covered AR Stent, distributor: First Medical Company [Global Medical Device Nomenclature Code 48136]). Both stent types come in a standard length of 120mm. Both of these stents are available and currently form part of the standard of care at GSH, although the stent selection is determined by stent availability and endoscopist preference – the conventional stent is generally favoured. Both are approved by SAHPRA as part of First Medical's list of approved devices they can import into and distributed in South Africa.

The technique of stent deployment will also be the same for both anti-reflux and conventional stents. Stent position and deployment success will be confirmed after stent placement, using water-soluble contrast injected through the stent under fluoroscopy – this will confirm the distal stent position crossing the OGJ. The patient will remain unaware of which type of stent they are receiving. The progress of the trial will be documented according to the CONSORT 2010 flow diagram[22].

Follow-up

Technical success of the stent insertion will be confirmed using fluoroscopy immediately after insertion. Any insertion-related complications will be documented. All patients will be appropriately observed in the gastrointestinal unit after the procedure and then admitted to the ward for overnight observation. They will undergo scintigraphy the following day (day 1 post the procedure) and then if deemed well enough will be either discharged home or referred back to their referring hospital. The follow-up period will subsequently continue for a total of 8 weeks.

Patients with palliative oesophageal cancer are in most instances frail and have a significantly limited life expectancy. It is thus imperative upon discharge, that further research-related follow-up should not inconvenience the patient nor have a negative effect on their quality of life. Furthermore, many of the patients treated at GSH have limited financial means to afford repeated follow-ups at the hospital. For these reasons, subsequent follow-up after discharge, will be done telephonically. Patients will be phoned at 1, 2, 4 and 8 weeks post stent insertion and will be asked about any symptoms related to the stent insertion, and have an assessment of symptomatic GOR using the GerdQ questionnaire [8], dysphagia, cough and pain levels at each telephonic follow-up. Telephonic follow-up of these patients will be done by the Clinical Coordinator, who is blinded to which type of stent the patient has received.

All patients will also be referred to the GSH Palliative Care Team. With any symptom reported by a patient or family member that is deemed to possibly require further intervention or treatment, the patient will be requested to return for an evaluation or appropriately managed according to the Palliative Care Distress Algorithm (Appendix 1). All complications will be managed as per standard treatment routinely employed for such a complication at GSH. Any such complications will be documented.

OUTCOME MEASURES

Primary Outcome Measure

The primary outcome will be patient-reported rates of symptomatic volume GOR and objectively measured volume GOR in both study groups. Patient-reported symptomatic volume GOR will be assessed using the validated GerdQ questionnaire (Appendix 2) [8]. This questionnaire has been chosen has it is simple, easy to understand and includes only 6 questions, which are all reflux-related. This questionnaire will be administered to the patient prior to the procedure, to establish a baseline. It will then subsequently be telephonically administered at the scheduled telephonic follow-ups at weeks 1, 2, 4 and 8. The GerdQ questionnaire enables the patient to provide a score at each follow-up interaction which can then be documented and the mean scores between the two groups can then be compared.

GOR will also be objectively measured on day 1 post stent insertion using scintigraphy. The proposed protocol for scintigraphy is described in Appendix 3. This modality has been chosen as its accuracy compares favourably to pH monitoring[9], but is much less invasive. It requires the patient to swallow a meal of soft, runny porridge and then undergo imaging. pH monitoring is invasive, requiring the insertion of an uncomfortable nasal probe which stays in-situ for 24 hours, increasing discomfort for the patient but also increasing the hospital stay by a further 24 hours. It is thus deemed inappropriate in this setting.

Secondary Outcome Measures

The secondary outcomes that will be assessed will include immediate technical success rate and any complications related to the stent insertion, subsequent stent-related complications, patient-reported dysphagia score prior to stent insertion, on day 1 post-insertion and then at each of the scheduled telephonic follow-ups and lastly, patient survival at 2 months post stent insertion. Dysphagia assessment will be done using the modified dysphagia scale first published by Mellow and Pinkas and validated for assessing dysphagia after metal stent insertion for oesophageal cancer (Appendix 4)[23]. Furthermore, an assessment of the patient's pain level and whether they are coughing will also be documented, using validated pain[24] and cough scores[25] and pain (Appendix 5 & 6).

Data Collection

The following data parameters will be collected:

- Age
- Gender
- Performance status25 and BMI of the patient at time of stent placement
- Histological type of malignancy (e.g. adenocarcinoma, squamous cell carcinoma or other)
- Reason for inoperability: metastases, locally advanced or poor performance status
- Position of oesophageal malignant stricture (endoscopic measurement in centimetres from the incisors)
- Patient-reported degree of dysphagia prior to stenting
- Patient-reported GerdQ score pre-stenting
- Stent characteristics: anti-reflux vs conventional, length, diameter and brand name of stent
- Immediate technical success rate
- Immediate stent insertion complications:
    - Bleeding
    - Perforation
    - Other

- Subsequent stent-related complications during the follow-up period:
    - Bleeding
    - Perforation
    - Migration
    - Stent occlusion and cause thereof
    - Other
- Quantitative assessment of volume reflux as per scintigraphy (on day 1)
- GerdQ score at follow-up at week 1, 2, 4 and 8
- Dysphagia score on day 1 post stent-insertion and at follow-up weeks 1, 2, 4 and 8
- Patient survival outcome at 8 weeks
- Cough and pain score pre-insertion, on day 1 and at 1, 2, 4 and 8 weeks

Data Safety and Monitoring

A password-protected computer-based registry will be created using REDCap (Research Electronic Data Capture). No paper-based data collection sheets will be used to record the data and analysis will take place directly from the registry after data exportation into an appropriate statistical software programme such as SPSS or Stata.

To protect patient confidentiality:

- Access to the registry will be password protected and will only be accessed by investigators on this study.
- Data extracted from the registry to SPSS / Stata will be anonymised and patient details will only be identifiable from their designated trial number.

Research Procedures and Data Collection Methods

All data will be prospectively entered into the electronic registry at the time of stent insertion and at the defined post-insertion follow-up periods. Patients will be contacted telephonically at the defined post-insertion follow-up periods by the Clinical Coordinator. Other than the scintigraphy, this study will require no biological specimens or further special investigations specifically for the purposes of the research project.

ETHICAL CONSIDERATIONS

There will be no additional risk, cost or investigations to the patients if they agree to be included in the trial. Patients will only be included in the study after being informed about the study and completing the consent form. Patient confidentiality will be maintained. The study will be conducted in accordance with:

- Guidelines for Good Clinical Practice (GCP) in the conduct of Clinical Trials in Human Participants in South Africa. Latest Edition, 2020 (released June 2021).
- The Department of Health: Ethics in Health Research: Principles Structures and Processes 2004
- The Helsinki Declaration.

All efforts will be made to publish the results in an international or local academic peer-reviewed journal and submitted for presentation at an appropriate national or international congress. Although the patients who are included in the study may not benefit directly from their participation, the results may help us manage future patients more effectively.

Description of risks and benefits

This study will incur no additional risks relating to the trial or research process to the participant. Oesophageal stenting is the palliative management of choice in malignant dysphagia. Anti-reflux stents as an intervention have been shown not to increase risks or safety concerns compared to conventional stents and have similar rates of dysphagia improvement compared to conventional stents. Procedure and stent-related risks will thus not be increased due to participation in this trial. Both stents form part of current standard of care. Insertion and post-insertion management of these patients will be the same as for any patient requiring oesophageal stenting for malignant dysphagia.

The addition of scintigraphy in assessing GOR on day 1 post-insertion, will require the patient to consume a soft porridge with a runny consistency containing a small volume of a radio-active substance (Appendix 2). Measurements are done using a gamma camera. Although this exposes the patient to ionising radiation, the doses are extremely small[27] and equate to similar background radiation exposure of living in a large city. Any theoretical deleterious effects of such radiation are considered negligible in this patient cohort with such a limited life expectancy. The investigation is thus not considered to result in additional risks to the patient.

Informed Consent

- Informed written consent for enrolling in the study will be taken by one of the investigators on the day the patient is recruited
- Consent will be taken in a closed consultation room with only the patient, the patient's family, nurse and investigator present
- Where decision-making capacity is questionable, the patient will be excluded from the study
- The patient will be given a consent form explaining their condition and the proposed study
- The consent form complies with the requirements stipulated in the University of Cape Town Human Research Ethics Committee (HREC) standard operating procedures
- The consent form is available in English, Afrikaans and isiXhosa
- Information contained in the consent form will be discussed with the patient and family members by the investigator
- The patient will be offered the option to take time to think about the information provided and discuss it with family members
- If the patient is unable to understand English then an investigator fluent in Afrikaans or Xhosa will consent the patient for the study. If an investigator fluent in the necessary language is not available then a translator will be used.
- Participation in the trial will be completely voluntary and it will be emphasized that if the patient does not wish to participate in the trial, the clinical management of their disease will not be affected in anyway and they also have the option to withdraw from the trial at any given point.

Privacy and confidentiality

Patient privacy and confidentiality will be upheld throughout the study period. All patient data will be stored on a password-protected registry, which will only be accessible to the investigators and data being analysed will be appropriately anonymised.

Reimbursement to Participants

Participants will not be reimbursed for their participation

Emergency care and insurance for research-related injuries

This trial is not studying a new or unapproved device and both interventions already form part of the standard of care for these patients at GSH, thus specific research-related risks are not considered

significant in this study, and specific research-related emergency care or insurance will not be needed. Any stent-related complications will be managed as per standard treatment protocols used by the GSH Upper Gastrointestinal Surgery Unit for any patient with an oesophageal stent complication. However, the University of Cape Town (UCT) has agreed to act as the Regulatory Sponsor for this trial and as the current directive from the UCT Risk Management Office stipulates that all clinical trials need no-fault insurance, UCT has agreed to provide such insurance cover for this trial (signed sponsorship agreement is submitted separately).

Care after Research

This trial will not involve a pharmaceutical product or device that requires repeated administration. Both stents are inserted as a once-off procedure and unless there is an unforeseen complication (such as stent migration or patient intolerance of the stent necessitating removal), these stents usually stay in-situ indefinitely. With the unfortunately short life expectancy for this group of patients, most participants will require a single stent insertion and will then die with the stent still in-situ. This means that once the trial period is over, they will still continue to have the benefit of the stent regardless of when the trial ends. If the anti-reflux stents are proven to significantly reduce GOR, those participants in the conventional stent group will however not be offered an anti-reflux stent if the stent they have received is still functional and without problems. This is because the procedure of exchanging one stent for another carries significant risks and in this vulnerable group of patients such a stent exchange procedure would not be justified.

Statistical Analysis

Data will be captured using the REDCap electronic data capturing software licensed to the University of Cape Town. All data exploration and analysis will be done using an appropriate statistical software programme such as SPSS (version 27.0, IBM, USA). Statistical significance will be set as $p < 0.05$. Recorded data will be expressed as mean (SD), or median (interquartile range) when non-normally distributed (continuous data). Where continuous data are non-normally distributed, variables will be logarithmically transformed prior to inclusion in multivariable statistical analysis. Dichotomous variables will be expressed as proportions or percentages. Baseline demographic and clinical characteristics between the anti-reflux stent and the conventional stent group will be compared using appropriate statistical tests based on the nature of the data as well as distribution thereof. GOR scores between the two groups will be assessed using inferential statistics with the hypothesis that the anti-reflux stent group will have reduced reflux compared to the conventional stent group. In addition, survival analysis will be performed with visual representation using Kaplan Meier curves.

Sample Size

Using a power calculation for comparison of two continuous data means in a superiority assessment (with GerdQ score means as the primary outcome assessed), assuming a 2-point reduction in GerdQ mean score between the two groups - mean GerdQ score of 9 in the conventional stent control group and a GerdQ score of 7 in the anti-reflux stent group - with a standard deviation of 3, with an alpha level of 5% and power set at 80%, a sample size of 72, with 36 in each arm, is required.

Correlating this to the previous randomised controlled trials, it is noted that these numbers are similar, but slightly higher than previous trials. With concerns that a number of these previous trials were underpowered, a slightly bigger sample size is deemed appropriate.

Time Frame

The study will begin as soon as HREC approval has been granted and the relevant registrations with SANCTR and clinicaltrials.gov have been completed. It is expected to run for 36 months. Interim analyses of the collected data will be performed at 12 and 24 months.

Budget

All research-related costs will be covered by the General Surgery and Surgical Gastroenterology Research Funds.

1. Stents:
   Both types of oesophageal stents (conventional and anti-reflux) are currently available at Groote Schuur Hospital and as they form part of the standard treatment of these patients, will not need to be purchased specifically for this research study.
2. Scintigraphy:
   R4000 per investigation x 72 patients = R288 000
3. Clinical coordinator:
   The clinical coordinator for this trial is already employed by the University of Cape Town and is very active in multiple research projects within the Surgical Gastroenterology Unit. She will thus not need to be renumerated specifically for her assistance in this trial.
4. Other Costs:
   This trial will not require specific electronic or other research-related equipment or major stationary costs. All other minor costs will be borne by the study investigators.

   TOTAL COSTS: R288 000

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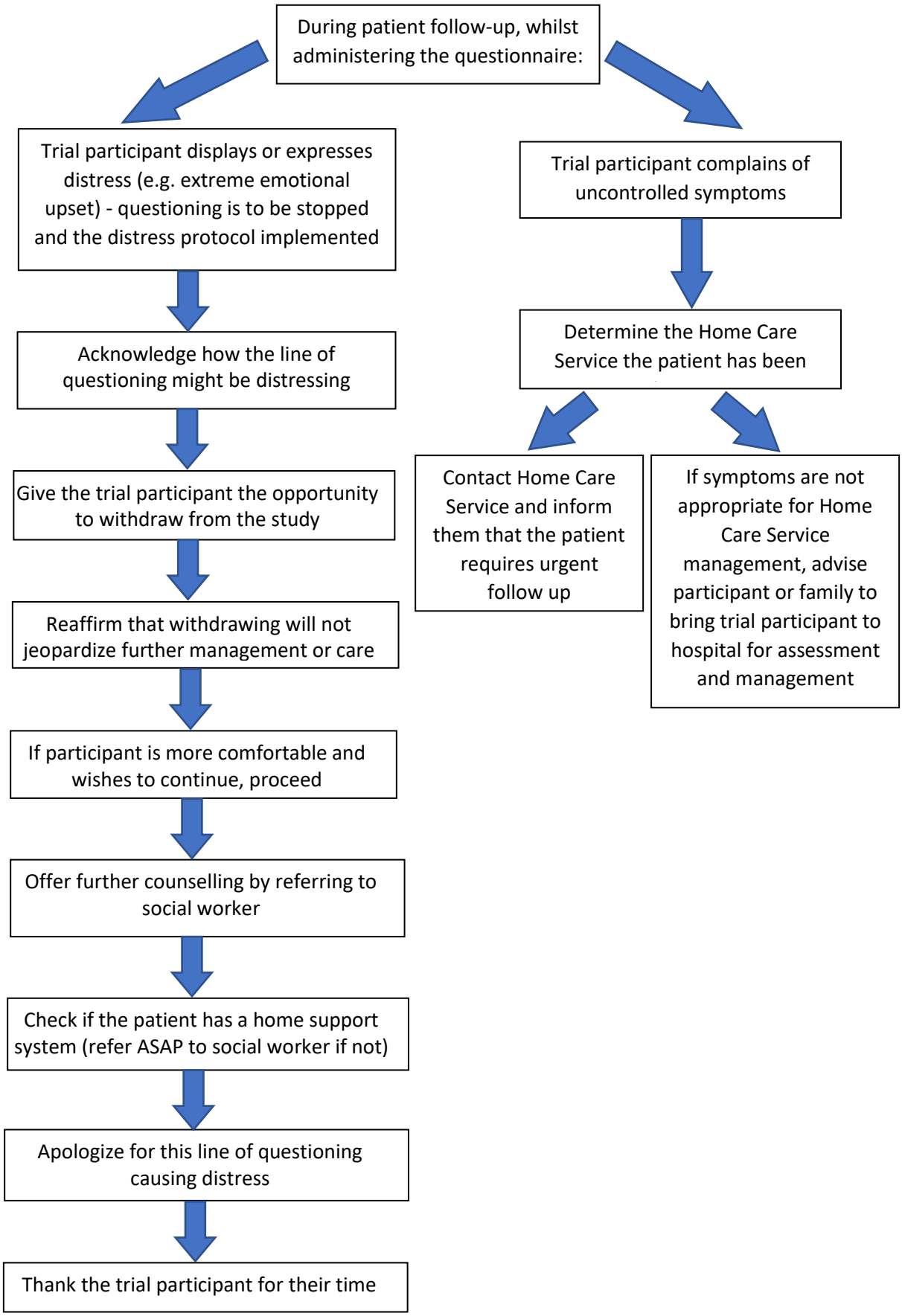
APPENDICES

List of Appendices

Appendix 1 : Palliative Care Distress Management Algorithm



Appendix 2: GerdQ score[8]

Question	Frequency score (points) for symptom			
	0 day	1 day	2–3 days	4–7 days
1. How often did you have a burning feeling behind your breastbone (heartburn)?	0	1	2	3
2. How often did you have stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)?	0	1	2	3
3. How often did you have a pain in the centre of the upper stomach?	3	2	1	0
4. How often did you have nausea?	3	2	1	0
5. How often did you have difficulty getting a good night's sleep because of your heartburn and/or regurgitation?	0	1	2	3
6. How often did you take additional medication for your heartburn and/or regurgitation, other than what the physician told you to take? (such as Tums, Rolaids, Maalox?)	0	1	2	3

Appendix 3: Gastro-oesophageal Scintigraphy Protocol

The following standardised protocol is provided by the Groote Schuur Hospital Nuclear Medicine Department for gastric emptying, including GOR assessment:

An Oats meal is given to the patient as part of the study:

- Prepare the Oats meal (soft, runny consistency) before taking the patient to the camera room
- Also prepare a small radioactive marker, using a small piece of cotton-wool, to put on the Xiphisternum.
- Once the radioactive meal has been prepared, take the patient to the camera room, and explain the procedure on how the patient must eat the radioactive meal, especially in line with Radiation Protection.
- Ensure that the patient details are entered on the acquisition station, that a workflow is ready for the first acquisition, and that the patient is ready for scanning.
- Remove the patient's clothing from the waist up and place the radioactive marker on the Xiphisternum of the patient. Give patient a gown to put on.
- Diabetic patients on Insulin (oral-insulin combo pts incl.): check how much Insulin the patient needs to take, the patient needs to take half the dose before eating the meal, irrespective if the patient took half a dose of Insulin earlier to lower the glucose.
- Give the patient an apron and a pair of gloves to put on, before handing the radioactive meal to the patient.
- The patient needs to finish the meal within 10 min.
- Immediately after the patient finished the radioactive meal, wipe the patient's mouth with paper towel or rinse the mouth, get the patient on the bed and immediately start imaging.
- Immediately after the completion of the meal, the patient is positioned in front of the camera. The study can be acquired on standing, sitting or supine.
- The same position should be used throughout the study with the camera heads at the same distance from the patient. Document all the

Radiopharmaceutical:

- **Radioisotope:** Technetium-99m (^{99m}Tc)
- **Pharmaceutical:** Tin-Colloid (SnColl)
- **Physical $T_{1/2}$:** 6.02 hours
- **Principle photo-peaks:** 140 keV
- **Dose:** 20-30 MBq

Imaging Protocol:

- **Collimator:** Low Energy High Resolution (LEHR)
- **Starting time post injection:** Immediately after the patient has finished the radioactive Oats meal.
- *Note: a new acquisition series needs to be opened for each acquisition!*

- **Static Acquisition:**
  - **Series:** *Name the acquisition series according to the time of imaging post last +swallow! The first image will be named the exact time after last swallow (e.g. STATIC 3min), and the rest of the images will be named according to the imaging protocol! (STATIC 0min [i.e. immediately after last swallow], 1hr, 2hr, 3hr, and 4hr)*
  - **Zoom:** 1.0
  - **Camera Preset:** Tc99m-NMG
  - **Detectors:** Both Detectors
  - **Time per view:** 60 sec
  - **View Labels:** Label each view according to patient-to-detector orientation, as well as the time post last swallow (e.g. **Detector 1:** ANT 5min, **Detector 2:** POST 5min).
  - **Orientation:** Head Out

- After the *STATIC **4hr*** image, show the Nuclear Medicine Physician to see if any further imaging is required.

Sources of Error:

- Vomiting after meal ingestion
- Poor labelling
- A nonstandard meal
- A marked variation in the environment, such as noise, lighting, or temperature during imaging. Emotional fluctuations, such as fear of the medical environment, anxieties about results, anger after a long wait for the study to begin

Suggested Standard Meal For Gastro-oesophageal Scintigraphy

- Jungle Oatso Easy 50g satchet
- Protifar 14g powder
- Sugar or Replace 10g *
- Boiling water 180 ml

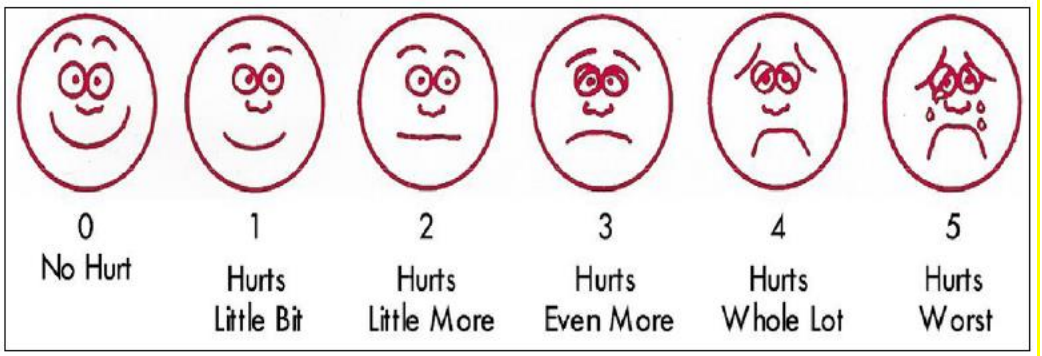
- Add boiling water to the dry ingredients
- Stir briskly
- Add and mix 20-30 MBq of Tc99m-Tin colloid

- *NOTE
- Replace is tasteless but provides the same amount of carbohydrate as sugar does. In order to adjust for individual patient sweet taste preference, the total (10g) sugar or Replace should always remain constant, but the proportion of each can be changed. For example:
- 5 g sugar + 5 g Replace
  OR
- 10 g sugar + 0 g Replace
  OR
- 0 g sugar + 10 g Replace

Appendix 4: Dysphagia Score[23]

- 0 = normal/no dysphagia
- 1 = ability to eat some solid food
- 2 = ability to eat semisolids only
- 3 = ability to swallow liquids only
- 4 = complete dysphagia (inability to swallow saliva)

Appendix 5: Pain Score – Visual Analog (Face) Score[24]



Appendix 6: Simplified Cough Score[25]

Score	Daytime Cough Symptoms	Nigh-time Cough Symptoms
0	No cough	No cough
1	Transient cough occasionally during the daytime	Transient cough before sleep or occasional cough during the night
2	Frequent cough mildly affecting daily life	Cough mildly affects night sleep
3	Frequent cough severely affecting daily life	Cough severely affects night sleep

Appendix 7 – Proposed Data Sheet

1. **Participant Trial Number**
2. **Patient/Tumour Baseline Characteristics:**
    - Age
    - Gender
    - Performance Status (ECOG)
    - Co-morbidities
    - Substance use
    - Body Mass Index
    - Histological type of malignancy (SCC, Adenocarcinoma, Other)
    - Reason for inoperability (metastases, locally advanced, poor performance status, or other)
    - Position of malignancy (endoscopic measurement in centimetres from the incisors)
    - Length of tumour
3. **Pre-stenting Scores:**
    - Dysphagia (pre-stenting)
    - GerdQ (pre-stenting)
    - Pain (pre-stenting)
    - Coughing (pre-stenting)
4. **Stent Insertion:**
    - Stent characteristics: anti-reflux vs conventional, length, diameter and brand name of stent

- Immediate technical success rate
- Immediate stent insertion complications:
    - Bleeding
    - Perforation
    - Incorrect stent placement
    - Other

5. **Day 1 Post-Stenting:**
    - Scintigraphy Results
        - Oesophageal Clearance
        - Oesophageal Reflux
        - Secondary Clearance
        - Gastric Emptying
    - Dysphagia score (day 1)
    - Pain score (day 1)
    - Coughing score (day 1)
6. **Week 1 Post-stenting:**
    - GerdQ Score (week 1)
    - Dysphagia Score (week 1)
    - Pain Score (week 1)
    - Coughing Score (week 1)
7. **Week 2 Post-stenting:**
    - GerdQ Score (week 2)
    - Dysphagia Score (week 2)
    - Pain Score (week 2)
    - Coughing Score (week 2)
8. **Week 4 Post-stenting:**
    - GerdQ Score (week 4)
    - Dysphagia Score (week 4)
    - Pain Score (week 4)
    - Coughing Score (week 4)
9. **Week 8 Post-stenting:**
    - GerdQ Score (week 8)
    - Dysphagia Score (week 8)
    - Pain Score (week 8)
    - Coughing Score (week 8)
10. **Outcomes:**
    - Stent-related complications during the follow-up period:
        - Bleeding
        - Perforation
        - Migration
        - Stent Occlusion and Cause Thereof
        - Perforation
        - Other
    - Survival outcome at 8 weeks (alive or dead)