A pilot randomised trial on the effect of Gaviscon Advance on laryngopharyngeal reflux symptoms in adults referred to an outpatient Speech and Language Therapy service

A thesis submitted to the University of Dublin in part requirement of the MSc Clinical Speech and Language Studies
August, 2022

Kate Grehan, BSc
Declaration

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Signed:

Kate Grehan
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I would not have been able to complete this dissertation without the endless support of my husband Michael. I cannot thank him enough for his motivation and belief in me. To my mother Cathy, my biggest cheerleader and supporter, thank you so much. And finally, I would like to thank my family and close friends, especially my dear friend Cathy, for all of their help and encouragement throughout.
Abstract

A pilot randomised trial on the effect of Gaviscon Advance on laryngopharyngeal reflux symptoms in adults referred to an outpatient Speech and Language Therapy service.

Kate Grehan

Background: Laryngopharyngeal reflux (LPR) can result in vocal tract symptoms and voice problems. The exact pathophysiology and prevalence of LPR is unknown. It can lead to a wide variety of symptoms, and as a result assessment and diagnosis can be challenging. There are a range of management options with a growing body of evidence to advocate for the use of sodium alginate in the treatment of LPR. Studies have examined the benefit of taking sodium alginate after a 2-to-6-month time period but none have examined the effect of taking sodium alginate over a shorter time period and whether this would still have a similar effect.

Aims: This research aims to explore the feasibility of conducting a study to explore the impact of Gaviscon Advance on symptoms of LPR amongst adults being referred to an outpatient Speech and Language Therapy department by their Ear, Nose and Throat (ENT) surgeon. The objective is to guide and inform a larger scale experimental study. In particular, this research aims to explore the feasibility of a waitlist study design, recruitment of participants, adherence to the study protocol and to monitor for any unforeseen circumstances.

Methods & Procedures: A pragmatic pilot trial was designed to explore the feasibility of a larger scale pragmatic randomised controlled trial (RCT). A pragmatic RCT was planned to be able to inform clinical practice. An RCT had not been conducted in this outpatient setting before and its practicality had to be established. Four participants were recruited by study gatekeepers while they were waiting their initial Speech and Language Therapy assessment and their participation ceased once they attended that assessment. Participants needed to score >13 in the Reflux Symptom Score (RSS) and meet the study eligibility criteria. Once recruited, participants were randomly assigned to the treatment group or the no-treatment control group. The treatment group was advised to take 10mls sodium alginate (Gaviscon Advance) after breakfast, lunch and dinner and again before bed. The no-treatment control group was advised not to change anything and that management would be discussed with them at their initial assessment. Both groups completed the RSS weekly to monitor for any changes in symptoms. A study diary was kept to record outcomes of study procedures and for any adverse events. Data were later extracted for analysis.

Outcome & Results: A smaller scale pilot trial in preparation for a full pragmatic RCT was completed. Two participants were randomised to each group. The waitlist study design seemed to be appropriate to answer the research aims. Recruitment was best facilitated by choosing a single gatekeeper, since that person could assume responsibility for actively managing prospective participants. The eligibility criteria were deemed to be too stringent and excluded participants whose medical history would otherwise permit them to safely engage with the study protocol. One participant found it difficult to adhere to the Gaviscon Advance protocol due to the taste. Most participants completed the RSS and study documents accurately, but some had difficulty completing and returning them to the principal investigator.

Conclusions: A full pragmatic randomised controlled trial is feasible, with some amendments to the original study protocol described.
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<th>Description</th>
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<tr>
<td>ENT</td>
<td>Ear, nose and throat</td>
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<tr>
<td>ID</td>
<td>Identification</td>
</tr>
<tr>
<td>ILO</td>
<td>Inducible laryngeal obstruction</td>
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<tr>
<td>GERD</td>
<td>Gastroesophageal reflux disease</td>
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<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>HEMII-pH</td>
<td>Hypo-pharyngeal-esophageal multichannel intraluminal impedance-pH</td>
</tr>
<tr>
<td>LPR</td>
<td>Laryngopharyngeal reflux</td>
</tr>
<tr>
<td>LPR-HRQL</td>
<td>LPR health related quality of life</td>
</tr>
<tr>
<td>MII-pH</td>
<td>24-hour multichannel intraluminal impedance-pH monitoring</td>
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<tr>
<td>PI</td>
<td>Principal investigator</td>
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<tr>
<td>PIL</td>
<td>Participant information leaflet</td>
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<tr>
<td>PPI</td>
<td>Proton pump inhibitor</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>REC</td>
<td>Research ethics committee</td>
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<tr>
<td>RFS</td>
<td>Reflux finding score</td>
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<tr>
<td>RSA</td>
<td>Reflux sign assessment</td>
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<tr>
<td>RSI</td>
<td>Reflux symptom index</td>
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<tr>
<td>RSS</td>
<td>Reflux symptom score</td>
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<tr>
<td>SLT</td>
<td>Speech and language therapist</td>
</tr>
<tr>
<td>TCD</td>
<td>Trinity College Dublin</td>
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<tr>
<td>URTI</td>
<td>Upper respiratory tract infection</td>
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1. Literature Review

1.1 Introduction
This study aims to explore the feasibility of a study examining the effect of sodium alginate (Gaviscon Advance) on laryngopharyngeal reflux (LPR) symptoms in patients referred to an outpatient Speech and Language Therapy department by their Ear, Nose and Throat (ENT) consultant. This first chapter gives an overview of the current understanding of the pathophysiology, symptoms and prevalence of LPR. The role of the Speech and Language Therapist (SLT) is explored along with roles of other members of the multidisciplinary team. Current methods of assessing, diagnosing and treating LPR are reviewed, with a detailed look at the role of sodium alginate, particularly Gaviscon Advance. This information offers a context and rationale for the current study. The specific research aims of this study are outlined at the end of the chapter.

1.2 Laryngopharyngeal reflux
There has been a growing body of research into the area of LPR in recent years (Lechien, Akst et al., 2019). Despite this increased interest into LPR, there is much that is still not understood about this condition, unlike the better-known Gastroesophageal Reflux Disease (GERD). Some researchers consider LPR and GERD to be distinct entities (Koufman et al., 2002), whereas others believe LPR to be an “extraesophageal variant of GERD” (Patel et al., 2018, p. 512). Therefore, there has been a variety of terminology used in the literature, which can make collation of research findings challenging. However, the term “laryngopharyngeal reflux” appears to be the most widely used in recent literature.

1.2.1 LPR pathophysiology
Although the exact pathophysiology of LPR is not clearly understood, two main theories have emerged and are generally accepted (Lechien, Akst et al., 2019; Krause et al., 2021). In the first, LPR is caused by direct reflux events of stomach contents such as bile and pepsin into the larynx (Sereg-Bahar et al., 2015; Pearson et al., 2011). As these contents have little or no acidic properties, patients rarely report typical GERD symptoms such as heartburn (Koufman, 1991). As a result, LPR can also be referred to as “silent reflux” (McGlashan et al., 2009, p. 244). The reflux of these gastrointestinal enzymes can result in mucosal changes, inflammation, epithelial thickening and microtrauma (Lechien, Saussez et al., 2017). Research has found that even minor or occasional reflux events of pepsin can be damaging to the sensitive laryngeal mucosal lining (Koufman, 1991; Johnston, 2011). The second theory hypothesises that reflux in the lower
oesophagus (as opposed to the larynx) can indirectly stimulate symptoms of LPR (Wright et al., 1990; Amarasiri et al., 2013). This is possible due to the shared innervation of the oesophagus and airway meaning that even if a reflux event is confined to the oesophagus, it could still provoke a laryngeal response (Smith & Houghton, 2013).

1.2.2 LPR symptoms
The symptoms of LPR can be nonspecific and differ from symptoms of GERD. Table 1.1 details reported symptoms within each condition (Koufman, 1991; Koufman et al., 2002; Lechien, Akst et al., 2019). Many of these overlap with symptoms of other conditions that can affect the laryngopharyngeal mucosa such as allergies, environmental irritants and poor vocal hygiene (Lechien et al., 2018; Ah-See et al., 2012). LPR tends to occur intermittently (Koufman et al., 1996) and it can also co-occur with GERD (Jaspersen et al., 2003). While the exact relationship between LPR and GERD is controversial, it is generally accepted that <50% of patients with LPR also have GERD (Lechien, Akst et al., 2019). LPR is suspected to be a factor in some upper airway symptoms such as coughing and wheezing (Pearson et al., 2011). Micro aspiration of gastric contents has also been observed in patients with LPR (Park et al., 2021).

Table 1.1: Common symptoms in LPR versus GERD

<table>
<thead>
<tr>
<th>LPR</th>
<th>GERD</th>
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<tbody>
<tr>
<td>• Hoarseness</td>
<td>• Heartburn</td>
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<tr>
<td>• Globus sensation</td>
<td>• Regurgitation</td>
</tr>
<tr>
<td>• Cough</td>
<td>• Erosive esophagitis</td>
</tr>
<tr>
<td>• Throat clearing</td>
<td>• Predominantly liquid reflux</td>
</tr>
<tr>
<td>• Excess mucous</td>
<td>• Supine (nocturnal) reflux</td>
</tr>
<tr>
<td>• Predominantly gaseous reflux</td>
<td></td>
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<tr>
<td>• Upright (daytime) reflux</td>
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1.3 Multidisciplinary management
1.3.1 General Practitioners
People who experience symptoms of LPR will usually attend their General Practitioner (GP) initially. It has been reported that knowledge about LPR amongst GPs in the UK is low (Karkos et al., 2007). Although a treatment algorithm has been suggested to assist GPs in managing patients with LPR (Lechien, Saussez et al., 2020), most will tend to refer on to specialist services for further evaluation and advice. Due to its heterogenous nature LPR can often be managed by a
variety of disciplines, all with different specialisms. Consensus reports in the literature on the management of LPR have included input from otolaryngology, gastroenterology and pulmonary medicine (Koufman et al., 1996).

1.3.2 Ear, Nose & Throat (ENT)
After they have been seen by their GP, a common pathway for patients with LPR is to be referred to an ENT consultant (Lechien, Saussez et al., 2020). ENT doctors will carry out a laryngoscopy for visualisation of their larynx and to exclude malignancy (Lechien et al., 2020). Some ENT consultants may query whether the patient is presenting with LPR. However, even where LPR has not been considered, patients may still have it. Research has shown that laryngoscopic findings suggestive of LPR are non-specific, have high interobserver variability and are often present in non-symptomatic people (Branksi et al., 2002; Lechien, Saussez, Schinder et al., 2019). In an international survey carried out on 824 ENT doctors, 37% of those surveyed felt less than knowledgeable about LPR, with variations in practices reported (Lechien, Carroll, Allen et al., 2021).

1.3.3 Gastroenterology
In the Gastroenterology literature, LPR can be referred to as an “extraesophageal variant of GERD” (Patel et al., 2018, p. 512). The first line of treatment amongst Gastroenterologists for suspected LPR is a 2-month trial of a proton pump inhibitor (PPI). If there is no improvement, it is suggested that patients be sent for pH monitoring. If pH testing is negative, then it is recommended that focus should be shifted towards treatment for functional laryngeal disorders with the use of neuromodulators or surgery (Patel et al., 2018; Arevalo et al., 2011). In a recent review of available literature, it was found that fundoplication surgery is an effective treatment for LPR and should be considered if medical management is not effective (Morice et al., 2022).

1.3.4 Respiratory
LPR can often lead to respiratory symptoms such as chronic cough and throat clearing (Smith & Houghton, 2013). Reflux is considered a trigger in patients with asthma (Harding, 2011). As a result, patients may be referred to Respiratory Consultants who might report suspected LPR from patient history and bronchoscopy results.

1.4 The role of the Speech and Language Therapist
SLTs have an important role to play in the assessment, differential diagnosis, management and treatment of voice and upper airway disorders (IASLT, n.d; RCSLT, 2019; Haines et al., 2021). Research has shown that voice therapy delivered by SLTs can be beneficial in managing voice
disorders from a variety of different aetiologies such as muscle tension dysphonia and vocal cord nodules (Carding et al., 2017). 

1.4.1 SLT-lead treatment

Voice therapy has been shown to be effective in treating symptoms of LPR in conjunction with other treatment approaches such as asthma therapy or anti-reflux therapy (Stachler et al., 2018) and has been encouraged in the literature on the management of LPR (Krause et al., 2021). Mucosal changes in response to LPR can be associated with the development of the vocal cord pathologies (Koufman et al., 2000). In comparison to healthy subjects, patients with LPR can present with significant voice disorders (Lechien, Fink et al., 2017) so SLTs are well placed to assist in management as part of the multidisciplinary team.

Selby et al. (2003) took a cohort of 13 patients with LPR and explored the effect of reflux treatment and voice therapy on perceptual and acoustic analysis of voice quality. Results showed a small improvement in the perception of voice quality post-treatment. However, this was a small sample size with no control group. Furthermore, 9 of the 13 participants were deemed to have mild LPR, therefore outcomes were likely to be less significant. Beech et al. (2013) reported significant improvements on the Reflux Symptom Score (RSS) for 34 participants with LPR and dysphonia when treated with voice therapy and a PPI. However again this study lacked a control group. Another study explored whether voice therapy in addition to omeprazole 20mg twice daily was superior compared to omeprazole 20mg twice daily alone. Outcome measures used were the Reflux Symptom Index (RSI), perceptual voice analysis and acoustic voice analysis (Vashani et al., 2010). The authors concluded that outcomes were better for people who received voice therapy in addition to reflux medication compared to reflux medication alone. However, a standardised assessment and treatment protocol were not used, so results were difficult to verify. A recent systematic review explored voice outcomes as a method of measuring response to treatment amongst people with LPR (Lechien, Fink et al., 2017). The authors reviewed studies of patients with a diagnosis of LPR based on symptoms lasting one month or more, patient reported symptoms and signs on laryngoscopy as well as a positive result on 24-hour multiple-probe pHmetry. Twenty-five studies were included which accounted for 1483 patients with LPR and 587 control subjects. The main voice assessment outcomes were hoarseness assessed by physicians or patients, followed by acoustic parameters. The quality of the studies included were deemed to be modest by the authors. The authors reported variable techniques for determining LPR diagnosis and a “myriad of treatment regimens” which meant that clear conclusions could not be drawn. However, they did note that voice quality measured via acoustic analysis appeared to improve across the studies reviewed. This finding suggested that voice quality could be an important outcome measure when treating people with LPR.
1.4.2 SLT and upper airway disorders

The role of the SLT in the management of upper airway disorders has recently been outlined (Haines et al., 2021), particularly in the management of inducible laryngeal obstruction (ILO) and chronic cough. Reflux is generally considered to be a common cause of chronic cough and ILO (Smith & Houghton, 2013). LPR can induce hyper-responsiveness of the larynx which is an underlying feature in these upper airway conditions (Spyridoulas et al., 2015). In this study, the RSI, Reflux Finding Score (RFS) and salivary pepsin test were used with patients with either chronic cough or ILO. Evidence of LPR was found in the majority of these patients by at least one of these measures. Another study conducted a retrospective chart review to investigate the relationship between LPR and chronic cough (Yeakel et al., 2020). While all 28 patients had findings consistent with LPR upon 24-hour pH impedance studies, 23 had additional risk factors for chronic cough such as asthma. However, the authors concluded that LPR is likely to be a contributing factor to chronic cough. Another study analysed patients retrospectively who presented to an ENT clinic with chronic cough. Fifteen patients were assessed using the RSI and laryngoscopy (Lieder & Issing, 2011). They were prescribed a PPI and Gaviscon Advance for 2 months. There was complete resolution of the chronic cough in 14/15 participants. However, this was a retrospective study with a small number of participants included.

1.5 Assessment and diagnosis of LPR

Assessment and diagnosis of LPR is challenging given the heterogeneity of symptoms. A variety of different assessment tools have been proposed with no one method being proven to be fully reliable.

1.5.1 24-hour impedance pH monitoring

24-hour multichannel intraluminal impedance-pH (MII-pH) monitoring is currently considered the best-known method of assessing for the presence of LPR. This testing uses a probe to detect liquid and/or gas reflux into the pharynx and oesophagus. It provides a reflux profile including the type (acid, weakly acid, non-acid reflux), frequency and timing (daytime or night-time) of the reflux. However, this is just a 24-hour snapshot of a person’s presentation so may not be entirely reflective of their LPR picture as LPR can often occur intermittently (Lechien, Mouawad, Bobin et al., 2021). Current impedance pH probes available are reported to lack reliability above the upper oesophageal sphincter (Park et al., 2021). Furthermore, there is no standardised diagnostic criteria and interobserver errors in interpreting reflux events have reported to be an issue (Zerbib et al., 2013). In practical terms, 24-hour MII-pH manometry is difficult to access, some patients may not tolerate it well and it can be expensive.
1.5.2 Visualisation of the larynx - Laryngoscopy

Endoscopic evaluation of the larynx is often completed by ENT doctors. The RFS was created by Belafsky et al. (2001) as a tool to assist with the diagnosis of LPR based on direct visualisation of the larynx. LPR can cause visible signs on the laryngeal mucosa such as granuloma, posterior commissure hypertrophy, laryngeal inflammation and excess mucous (Belafsky et al., 2001; Lechien, Rodriguez Ruis et al., 2020). As with symptoms of LPR, visible signs of LPR are varied and non-specific. LPR associated findings have been found on laryngoscopy in people without LPR (Hicks et al., 2002). Concerns have been raised about the reliability and validity of the RFS. Authors have found only fair interrater reliability, modest intra-rater reliability and no correlation between the RFS and 24-hour pH impedance testing (Vance et al., 2020). The Reflux Sign Assessment (RSA) has recently been proposed in the literature as a more robust tool to evaluate laryngeal and extra laryngeal physical findings associated with LPR but further studies are required for validation (Lechien, Rodriguez Ruiz et al., 2020). In this study’s current context, neither the RFS nor RSA are used routinely in clinical practice amongst referring ENTs.

1.5.3 Digital scintigraphy

A novel digital reflux scintigraphy technique has been developed which has the potential to visualise reflux events as they occur (Park et al., 2021). Radio-labelled technetium-99m phytate is ingested and its presence in gastric reflux can be directly visualised. Digital reflux scintigraphy was found to be strongly positive in a cohort of patients with LPR and correlated with MII-pH results. While this tool is reported to be quick and well-tolerated, it cannot detect whether the reflux events were acidic or not. This is important information in considering the management of patients with LPR as reflux acidity can indicate different management pathways (Lechien, Mouawad et al., 2019).

1.5.4 Empirical treatment for diagnosis

The first line of treatment for GERD is with proton pump inhibitors (PPIs). PPIs aim to decrease acid secretion in the stomach (Ahmed & Clarke, 2022). As LPR was initially considered to be a manifestation of GERD, empirical trials of PPIs have long been the primary treatment option (Ford, 2005; Gupta et al., 2016). However, recent research suggests that this is no longer best practice. PPI medication does not prevent reflux from happening, so harmful gastric contents such as bile and pepsin may still be present and active even if a person is taking a PPI (McGlashan et al., 2009). In a recent randomised controlled trial (RCT), no evidence of benefit was found from taking a PPI as rated on the RSI in patients with persistent throat symptoms. These authors caution that inappropriate use of PPIs is a major concern and can contribute to potential polypharmacy, a risk of side effects and a risk of drug interactions (O’Hara et al., 2021). Systematic reviews and meta-analyses have concluded that there is no benefit (Liu et al., 2016) or very mild superiority
in using PPIs in the management of LPR over placebos (Lechien, Saussez et al., 2019; Guo et al., 2016). More recently, a systematic review of available systematic reviews was conducted by Cosway et al. (2021). These authors became concerned about the poor standard of systematic reviews concerning the use of PPIs for LPR. They critically appraised ten systematic reviews and found nine to be at high risk of bias. The one study that was at low risk of bias did not find a benefit of PPIs in persistent throat symptoms (Chang et al., 2011). The authors concluded that the methodological flaws in the systematic reviews mean limited conclusions can be drawn about the use of PPIs in persistent throat symptoms. They highlighted the importance of rigorous and sound systematic reviews and for these to be scrutinised before being published as they attract a large number of citations and can lead to misinterpretation and a negative clinical impact.

1.5.5 Pepsin detection
The presence of the stomach enzyme pepsin in the laryngeal structures has been thought to contribute to an inflammatory response (Lechien, Saussez et al., 2017). The Peptest device (RD Biomed Ltd., Hull, United Kingdom) has been developed to measure saliva pepsin concentration to assist in the diagnosis of LPR. This tool is reported to be easy to use but it has still not been validated (Lechien, Saussez et al., 2017). One study explored the usefulness of the Peptest on patients with an RSI score >13 who had had a laryngoscopy to rule out an infection or pathology. The authors included 221 participants and found that a positive result on the Peptest had a high likelihood of LPR (likelihood ratio of 9.61). They encouraged use of this test as a simple, inexpensive, non-invasive and easily reproducible way in the absence of more complex testing like MII-pH manometry and instead of empirical trials of PPI (Barona-Lleo et al., 2018). In a study of therapeutic response to treatment of 124 patients with LPR diagnosed by hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMII-pH), 90 participants had a positive Peptest result. Although those that had a positive Peptest result had better improvements in digestive and respiratory symptoms as measured on the RSS, the results were not significantly associated with reflux events (Lechien, Bobin, Deuanter et al., 2021). Another study that explored the relationship between hypopharyngeal reflux events and saliva pepsin concentration found no significant association between reflux events and saliva pepsin concentration (Lechien, Bobin, Dapri et al., 2021). Similarly, researchers did not find a significant correlation with LPR symptoms using patient self-reported outcome measures and saliva pepsin levels but reported that a lack of correlation did not mean lack of pathophysiological effect (Jung et al., 2017). Another tool using the Restech measurement system (Dx-pH) has been developed which measures oropharyngeal pH. However, diagnostic accuracy of this tool compared to saliva pepsin measurement is limited (Weitzendorfer et al., 2020). Future research into the impact of other substances such as bile salts and trypsin should be investigated in addition to pepsin (Lechien, Bobin, Dequanter et al., 2021).
1.5.6 Self-rating tools in the assessment of LPR

In the absence of a definitive diagnostic test for LPR, patient reported symptoms have become a primary method to identify patients presenting with LPR and for monitoring treatment outcomes (Francis et al., 2016). Furthermore, objective assessment tools such as MII-pH and scintigraphy are not readily available in most clinical settings. In addition, studies have found that 24-hour MII pH manometry does not correlate with patient reported symptoms and QOL (Kim et al., 2017). For SLTs working in settings with limited or no access to instrumental diagnostic tools, patient self-rated tools are important in the assessment and management of a patient’s voice and vocal tract complaints. Subjective patient self-rating tools are advocated for in the assessment of dysphonia (Dejonkere et al., 2001; Patel et al., 2018) and have the ability to shed light on whether a person is likely presenting with symptoms of LPR (Watson et al., 2013).

The RSI was designed and validated by Belafsky et al. (2001). This nine-item tool has been used widely both in the literature and in clinical practice as a self-rated tool in the assessment of LPR. The RSI in addition to the RFS was found to be comparable to 24-hour MII-pH monitoring in diagnosing LPR (Wan et al., 2014). While the RSI has some strengths, it is reported to have poor specificity and have overlap with non-reflux related throat conditions (Francis et al., 2016). The ability to overestimate LPR using the RSI has also been reported (Nacci et al., 2018). It has also been proposed by some researchers that the tool may not be robust enough to capture all the possible symptoms of LPR (Lechien, Bobin, Muls, Thill et al., 2020). These authors reviewed the available self-rated tools and found none considered all possible symptoms attributable to LPR. Therefore, they developed the 22-item Reflux Symptom Score (RSS) to encompass all possible symptoms of LPR based on expert opinion and the literature (Lechien, Bobin, Muls, Thill et al., 2020). They included sections on GERD symptoms as well as respiratory symptoms. They concluded that their findings correlated positively with the RSI scores.

1.5.7 LPR prevalence

As a result of this varied clinical presentation and difficulty with diagnosis, the exact prevalence of LPR is still unknown (Lechien, Mouawad et al., 2021). Some studies have reported a prevalence of 10% of outpatients presenting to otolaryngology clinics (Koufman, 1991) and 73% of patients with dysphonia (Koufman et al., 2000). However, these studies used pH monitoring to detect reflux events. This method is not sensitive in detecting non-acid or mixed acid reflux, which is reported to be found in up to 50% of patients with reflux (Lechien, Bobin, Muls, Eisendrath et al., 2020). Other studies used the RSI alone to estimate that 18.8%, 5% and 30% of the Chinese, Greek and British populations respectively show signs of LPR (Lam et al., 2006; Spantideas et al., 2015; Kamani et al., 2012). However, these studies did not use other diagnostic measures to determine the presence of LPR or rule out other airway pathologies. The prevalence of GERD
which is better understood and documented is approximately 20-30% of the US population (Ciprandi, & Gelardi, 2018).

1.6 Treatment of LPR

1.6.1 Diet and lifestyle
There is consensus in the literature that dietary and lifestyle advice are important for long term management of LPR (Krause et al., 2021; Huestis et al., 2020; Min et al., 2019). A recent study categorised commonly consumed foods and fluids in Europe by their refluxogenic potential to be able to advise patients with LPR on items to avoid, some of which are outlined in Table 1.2 (Lechien, Mouawad et al., 2021). One study explored the impact of an “alkaline” Mediterranean diet based on plant proteins, cooked vegetables and low levels of animal fats versus PPI on symptoms of LPR and the two treatment approaches were found to be comparable. It has been suggested that diet alone may be enough to manage most mild to moderate LPR, saving healthcare costs and unnecessary medication exposure (Zalvan et al., 2017).

Table 1.2: Some common foods and beverages considered to be very high refluxogenic items

<table>
<thead>
<tr>
<th>Avocado</th>
<th>Bacon</th>
<th>Alcohol - liquor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chocolate</td>
<td>Mayonnaise</td>
<td>Apple juice</td>
</tr>
<tr>
<td>Croissant</td>
<td>Macadamia nut, cashew nut, hazelnut</td>
<td>Beer</td>
</tr>
<tr>
<td>Curry</td>
<td>Olives</td>
<td>Citrus juices e.g. orange</td>
</tr>
<tr>
<td>French fries</td>
<td>Butter</td>
<td></td>
</tr>
<tr>
<td>Ice cream</td>
<td></td>
<td>Soda</td>
</tr>
</tbody>
</table>

1.6.2 Proton pump inhibitors
Although research has shown little support for superiority of PPI use over placebo, they are still commonly prescribed by referring ENT consultants (O’Hara et al., 2021).

1.6.3 Sodium alginate
Sodium alginate has been proposed as a treatment option as it forms a mechanical antireflux barrier on top of stomach contents (Sweis et al., 2013; McGlashan et al., 2009). While PPIs reduce the acidic properties of reflux, sodium alginate works to prevent reflux entering into the oesophagus and the larynx (McGlashan et al., 2009). When sodium alginate comes in to contact with the acidic gastric environment, the substances interact to form a “strong, coherent, voluminous, buoyant alginate raft” (Bor et al., 2019, p. S113). Alginates can form this raft over the stomach contents for up to 4 hours (Lechien, Mouawad et al., 2019). Alginates have the added benefit of having a non-systemic and physical rather than pharmacological mode of action (Bor
et al., 2019). Gaviscon Advance which contains 1000mg sodium alginate as its active ingredient has been shown to be effective when taken in 10ml volumes four times daily: once after each main meal (breakfast, lunch and dinner) and again at bedtime (McGlashan et al., 2009). Participants in this RCT were recruited from an Otolaryngology outpatient department who had a score >10 on the RSI and >5 on the RFS based on fiberoptic examination of the larynx. Participants were then randomized to either the treatment or control group. Participants in the treatment group were advised to take Gaviscon Advance as per the protocol. Participants in the control group had no treatment, so study blinding was not feasible as there was no placebo option. It is not clear from this study how the authors decided on this particular treatment protocol. To minimize assessment bias, assessors of the laryngeal examinations were blinded to the treatment group of the participant. All participants in the study were provided with vocal hygiene, dietary and lifestyle advice. A follow up assessment was completed at 2 months, 4 months and 6 months. Although there was a placebo effect observed in this study, the treatment group showed statistically significant improvement in RSI scores after 2 months. The authors found that improvements in RSI scores at 2 months were maintained at 6 months which indicated that Gaviscon Advance treatment of LPR can result in rapid symptom improvement when compared to PPIs over a similar time frame.

Although this study provides important information on the use of Gaviscon Advance in the management of LPR, there are some limitations. The authors used a cut off score of >10 on the RSI and >5 on the RFS, where these tools stipulate >13 and >7 respectively. So some participants may have been included that did not meet the validated criteria for LPR based on these tools (Belafsky et al., 2002; Belafsky et al., 2001). McGlashan et al. (2009) reported that 30 patients randomized to each group would have provided adequate power for between group comparisons at month 2. However, there were only 49 patients recruited, 24 to the treatment group and 25 to the control group. At month 2, 45 participants attended for follow up, 22 in the treatment group and 23 in the control group. Furthermore, there was a marked drop off rate to 33 participants at month 4 and 29 participants at 6 months. While this drop off was recorded, there was no reason given to explain this study attrition. The authors recorded six events that were considered to be severe, one of these in a patient taking Gaviscon Advance. Most of these adverse events was severe GERD. For the patient taking Gaviscon Advance they reported pain in extremity as the adverse event. The authors concluded that this pilot RCT showed that Gaviscon Advance is well tolerated and is effective in improving signs and symptoms of LPR compared with a control group. To date, no study has been conducted to explore improvement in LPR symptoms on this Gaviscon Advance protocol earlier than at 2 months. Another RCT was conducted to explore Gaviscon Advance compared to PPI (omeprazole) for patients with non-erosive reflux at 14 days and 28 days. Both treatments were found to be comparable but patients included in the study
needed to have heartburn or regurgitation as their main symptom on non-standardized tools, so the study population was likely not entirely representative of an LPR population (Chiu et al., 2013).

Wilkie et al. (2018) found that a treatment based on the use of sodium alginate (Gaviscon Advance) alone was comparable to a combined treatment of Gaviscon Advance and a PPI. Seventy-two participants were recruited for study. All participants were advised to take Gaviscon Advance four times daily, similar to McGlashan et al. (2009). The authors acknowledged that there was no randomisation in their study which was a limitation and a potential source of bias. The authors relied on patient reported RSI >10 as the sole outcome measure and while they acknowledge its weaknesses as a tool, they felt that in the context of treating LPR, patients’ perceptions of their symptoms were of greater clinical relevance than findings on endoscopy. Indeed, studies have shown that laryngoscopic findings do not always correlate with patient reported throat symptoms (Powell & Cocks, 2013).

Another RCT concluded that although sodium alginate (Alginos Oral Suspension) reduced symptoms of LPR and was well tolerated, it was not able to show superiority over placebo (Tseng et al., 2018). The study recruited 80 participants using the RSI and RFS. It also assessed LPR using MII-pH manometry. Like Gaviscon Advance, the active ingredient in Alginos Oral Suspension was 1000mg sodium alginate. However, Gaviscon Advance has the additional active ingredient of 200mg potassium hydrogen carbonate. Therefore, this difference in composition may have contributed to findings. In addition, this study protocol advised 20mls sodium alginate three times daily after meals and those in the control group took a placebo version. Gaviscon Advance has also been shown to be effective as an add-on therapy for people with inadequate response to PPI compared to a placebo treatment, but the diagnosis of LPR in this study was determined by a non-standardised questionnaire (Reimer et al., 2016).

**1.6.4 LPR impact on quality of life**

LPR has been found to impact on a person’s social and occupational functioning as well as perceived health, well-being and vitality (Carrau et al., 2005). In a study of patients with GERD both with and without LPR, the authors concluded that people with both GERD and LPR experienced greater disease burden and sickness-related absences from work compared to people with GERD without LPR (Gong et al., 2017).

As symptoms are so varied, LPR can be difficult to diagnose and patients tend to have multiple appointments with a variety of specialists before a diagnosis is made. This leads to an increased cost adding to patient burden. Francis et al. (2013) reported an estimated cost of $5432 per patient
in their first year of being evaluated for LPR in the United States as a result of consultations, examinations and medication consumption. Patients may also be sent for tests that do not yield appropriate outcomes which further delays diagnosis. For example, patients may be sent for a barium swallow to assess for LPR, which is no longer considered an appropriate diagnostic test (Watson, 2011).

Moreover, once LPR has been diagnosed, treatment time and response to treatment can vary. Some patients experience little or no response to treatment leading to unsatisfactory outcomes and prolonged treatment times of more than 6 months (Lechien, Saussez et al., 2020). These factors are likely to have a negative impact on a person’s QOL and therefore this is an important area for clinical research.

1.8 The purpose of this research

There is a growing body of evidence into the management of LPR symptoms which can impact greatly on a person’s QOL. SLTs are well placed to facilitate assessment and management of these symptoms. SLTs carry out assessment following voice assessment guidelines (Dejonkere et al., 2001), by reviewing the written ENT referral information and by relying on self-rated questionnaires. As there is no definitive objective assessment to diagnose LPR, SLTs can use validated LPR specific self-rating tools such as the RSS in determining whether a person is likely to be presenting with LPR.

SLTs can provide education on LPR as well as diet modification, lifestyle changes and the use of sodium alginites. In this current outpatient hospital setting, people taking Gaviscon Advance as per McGlashan et al. (2009) have been observed to report improvement in their symptoms sooner than the 2-month time frame as suggested by the authors. To date, no studies have looked at the effect of Gaviscon Advance for LPR at shorter intervals. From their study, Lechien, Saussez et al. (2022) concluded that a 6-week therapeutic response as measured on the self-rated RSS was predictive of the 6-month therapeutic response. This could have important implications as medication could be reduced at this 6-week mark in patients that are responding well, meaning they would not need to be on medications longer term and thus reduce the risk of any potential drug related adverse events.

To undertake a research project like this, it is important that practical concerns and feasibility of the study are carefully considered. There is much that is not understood about LPR, so it is important to ensure that the study is well designed with careful consideration given to ensure smooth running of the study process for both staff and participants. Pilot studies of this nature are
valuable in providing this information in the planning and justification of RCTs which will lead to higher quality RCTs (Lancaster et al., 2004).

1.9 Research aims

The aim of this pilot trial was to examine the feasibility of conducting a larger scale study to explore the effects of Gaviscon Advance on LPR symptoms in adults who were referred to an outpatient Speech and Language Therapy service by their ENT consultant. The research aimed to explore the feasibility of a larger study by looking at the study design, recruitment and adherence to study protocols. This was in preparation for a full study which aims to explore the effects of taking Gaviscon Advance four times daily for a period of up to 8 weeks, at weekly intervals. Specifically, the full study aims to explore how long patients need to take Gaviscon Advance in order to notice a clinically significant reduction in their LPR symptoms based on the self-rated RSS and whether their symptoms continue to improve over time. In addition, the full study will explore whether there is a statistically significant difference in improvements between patients who took Gaviscon Advance and those that did not.

A clear list of objectives and aims for a pilot trial are vital (Lancaster et al., 2004). In this pilot trial, the primary research aims were as follows:

Study design:
1. To investigate the feasibility of a waitlist study design.

Recruitment:
2. To explore how many eligible patients referred to the outpatient SLT service were enrolled in the study during the 3-month pilot time frame.
3. To determine whether the eligibility criteria used for participants were too broad or too narrow by reviewing recruitment rate and reasons for exclusion.

Adherence to the protocol
4. To investigate adherence to taking Gaviscon Advance and for both groups in completing the weekly RSS.

Unforeseen circumstances
5. To catalogue any unforeseen circumstances that act as barriers or facilitators to this research in terms of study design, recruitment or analysis.
2. Methodology

2.1 Introduction
This chapter aims to outline the methodology used to answer the research aims. The study design will be discussed and information will be provided on the participant characteristics. The chapter describes study materials used as well as the data collected, with explorations of the ethical considerations of the study. CONSORT was used to guide study reporting (Moher et al., 2012; Eldridge, Chan & Campbell et al., 2016; Zwarenstein et al., 2008).

2.2 Study design
The feasibility of conducting a randomised controlled trial (RCT) to examine the relationship between Gaviscon Advance and laryngopharyngeal (LPR) symptoms based on the Reflux Symptom Score (RSS) was explored. The study design chosen was a randomised controlled pilot trial. This pilot trial was conducted to inform a future, definitive RCT (Zwarenstein et al., 2008). It has been suggested in the literature that pilot trials should use both qualitative and quantitative data when planning larger trials (Baldeh et al., 2020). Quantitative data was obtained to explore study design, recruitment to the study and adherence to the study protocol. Qualitative data was collected to allow for exploration of any unforeseen barriers or facilitators to this pilot trial. This information will inform the full RCT, which will use a quantitative methodological framework. A quantitative experimental design will be able to tightly control the variables of interest. Research questions that seek to explore an intervention, such as Gaviscon Advance, are best answered with a randomised controlled design (Greenhalgh., 2014). The main objective of the definitive RCT will be to guide clinical practice in the current outpatient setting by comparing the outcomes of taking Gaviscon Advance versus no treatment in the management of symptoms of LPR. As such, the definitive RCT will be a pragmatic RCT which aims to look at the effectiveness of an intervention in usual care settings as opposed to explanatory RCTs that explore the efficacy of an intervention under optimal settings (Zwarenstein et al., 2008). Exploring these research objectives would not have been possible in an observational study. Furthermore, the lack of experimental studies into the effect of Gaviscon Advance on symptoms of LPR mean that the research questions could not be answered by a systematic review of existing literature.

Pilot trials are smaller versions of the main RCT and are carried out to determine whether the components of the main study are realistic and will work together (Eldridge, Lancaster & Campbell et al., 2016). The term “pilot trial” has been suggested when referring to a “study in which a future definitive RCT…is conducted on a smaller scale” (Eldridge, Chan & Campbell, 2016 p.2) and this term will be used throughout this manuscript. This pilot trial was designed to ensure the main processes of the RCT such as the study design, recruitment and adherence to the
study protocols all functioned and ran smoothly. Pilot trials can help identify unforeseen issues and problems, such as outcome measure tools being interpreted in unintended ways or not being completed sufficiently (Viechtbauer et al., 2015). Any unforeseen circumstances were recorded for later data extraction and analysis. The results of the pilot trial were intended to support decisions about whether to re-design, amend or progress as planned with a definitive RCT.

2.2.1 Waitlist study design

All new voice referrals from any Ear, Nose and Throat (ENT) consultant to the outpatient Speech and Language Therapy (SLT) service were contacted by a gatekeeper to see if they would be interested in participating in the study while they waited for their initial SLT appointment. Their participation in the study lasted up to a maximum of 8 weeks, by which time their appointment would be guaranteed. Waitlist design studies have an ethical advantage in that participants may access treatment sooner, but care must be taken not to overestimate treatment effects (Cunningham et al., 2013).

The pragmatic nature of the pilot trial meant that the study design was based on real-world practice which could be clinically applicable to the outpatient hospital setting, therefore a waitlist design was deemed to be the most appropriate (Zwarenstein et al., 2008). As waiting times for initial SLT assessments could fluctuate, this had to be reflected in the chosen time frame of the study. When the service was quieter or if there were cancellations, patients could be seen within 1-2 weeks. However, when the service was busier, patients may have to wait up to 8 weeks. This reflects the reality of a dynamic service that must adapt in response to changes in resources, staff leave or an increase in patient referrals. In clinical practice patients taking Gaviscon Advance protocol often report improvements in LPR symptoms before a full two months, as was proposed by McGlashan et al. (2009) and this information would be captured with this waitlist study design.

If the length of the study had been fixed at a longer time frame, it may have been less appealing for patients to participate and would not be ethical if it resulted in a delay to their initial SLT assessment, particularly for those in the control group. In addition, participants had not had any other SLT input regarding vocal hygiene or lifestyle advice at this point, therefore minimising confounding factors on study outcomes. A waitlist design was also decided upon as it was hypothesised patients would be motivated to participate as they had sought out SLT assessment. If recruitment was to commence after initial SLT assessment, this may be less appealing to patients as they may not want to risk being assigned to the control group and not be offered treatment for their symptoms. It would also raise ethical concerns as treatment would be withheld despite reports of LPR following full assessment. Despite the advantages of a waitlist design, it
is acknowledged that it may be a challenge to ensure sufficient data at later weeks which is one of the areas explored in this pilot trial.

2.3 Participant characteristics
Participants were all community dwelling adults over the age of 18. They had been referred to SLT from their ENT consultants for a variety of vocal pathologies and presentations. The duration and severity of the participant’s dysphonia and their specific vocal pathologies were not controlled for. As signs and symptoms of LPR are not clearly defined and can be variable, all patients were who were referred to SLT for a voice assessment were invited to participate, so as not to miss any suitable candidates.

2.3.1 Inclusion and exclusion criteria
The inclusion and exclusion criteria used were similar to the criteria used by McGlashan et al. (2009) (Table 2.1). These criteria were reviewed with criteria used in other studies exploring the effect of alginates in patients with LPR and in considering the patient population in the outpatient clinical setting. The rationale behind using these criteria was to exclude those participants who had a more serious underlying condition than LPR. For example, someone with a severe gastrointestinal illness may require more specialised Gastroenterology assessment and management. They were also chosen to exclude anyone for whom Gaviscon Advance may have been contraindicated to avoid any potential risk of harm. Furthermore, they were chosen to try to minimise the possibility of confounding factors on study outcomes. However, as pragmatic RCTs do not require eligibility criteria to be too stringent, one of the aims of this pilot trial was to explore whether these criteria were appropriate. The criteria were reviewed with participants during the eligibility phase of the study based on patient report and on their medical history from the ENT referral letter or hospital records.
### Table 2.1: Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults above 18 years</td>
<td>Only adults above the age of 18 were accessible within the study setting.</td>
</tr>
<tr>
<td>Score above 13 on the Reflux Symptom Score during eligibility phase</td>
<td>A score above 13 on the RSS is indicative of laryngopharyngeal reflux (Lechien, Bobin, Muls et al., 2019).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>Cigarette smoking could result in similar symptoms to LPR such as hoarseness, so participants who smoked were excluded to ensure it was not a confounding factor.</td>
</tr>
<tr>
<td>Clinically significant neurological illness</td>
<td>This included people with a cognitive impairment, diagnosis of Dementia or any person that may have found it challenging to complete the weekly questionnaires because of a neurological illness.</td>
</tr>
<tr>
<td>Significant gastrointestinal illness</td>
<td>Taking Gaviscon Advance with a significant gastrointestinal illness could be contraindicated.</td>
</tr>
<tr>
<td>Upper respiratory tract infection in the past 1 month</td>
<td>Symptoms of upper respiratory tract infections (URTI) could present similarly to LPR so people who had had an URTI were excluded to ensure it wasn’t a confounding factor.</td>
</tr>
<tr>
<td>Significant dysphagia</td>
<td>This referred to a person who was on modified food, modified fluids or required alternative methods of feeding for whom taking Gaviscon Advance would be unsafe or contraindicated.</td>
</tr>
<tr>
<td>Taking anti-reflux medication e.g. proton pump inhibitor or alginate</td>
<td>Existing anti-reflux treatments may interfere with outcome measures</td>
</tr>
<tr>
<td>On a salt restricted diet</td>
<td>The maximum daily dose of Gaviscon Advance is equivalent to 21% of the recommended daily intake for sodium which could be contraindicated for people on salt restricted diets.</td>
</tr>
<tr>
<td>Undergoing any other medical investigations/ treatment for their reflux symptoms</td>
<td>People who were undergoing other investigation for their symptoms were excluded to ensure there wasn’t another possible reason for their symptoms.</td>
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</table>

#### 2.3.2 Sample size calculation
Sample size calculation using G* Power indicates that a sample size of 84 participants will be needed to detect a large effect size in the future RCT (d=0.8) (Department of Psychology, 2019). Sample size calculations are not deemed essential for pilot trials (Eldridge, Chan & Campbell et al., 2016). However, some researchers suggest that the sample size for a pilot trial should be at
least 9% of the main RCTs sample size (Cocks & Torgerson, 2013). Using that method, 7.56 participants should be recruited to the current trial. This figure was used as a guide along with the principal investigator’s (PI) knowledge of the service’s referral rates as well as the allocated trial period of three months. A sample of five participants was decided upon as a realistic sample size to provide enough information on the RCT design and procedure. It was also hypothesised that there would be a likelihood of at least one person being allocated to each group with this number of participants. One of the aims of this pilot trial was to explore how many eligible participants were recruited, to inform planning for the RCT.

Figure 2.1: Pilot trial sample size proposal

2.3.3 Sampling method
Convenience sampling was used to recruit participants to the first stage of the study, which screened for eligibility using the RSS. This type of sampling was the most convenient in this setting and was chosen to try to recruit as many participants as possible in the limited time frame available. Convenience sampling is often used in health research and where there is a limited time in which to recruit participants (Bowling, 2014). Despite these advantages, convenience sampling is a type of non-probabilistic sampling, so it is less favourable than probabilistic study sampling.

2.4 Recruitment

2.4.1 Recruitment to eligibility phase
All new voice referrals from any ENT consultant to SLT service were contacted by a gatekeeper to see if they would be interested in participating in the study while they waited for their initial SLT appointment. The gatekeeper was a member of the administrative team working in the hospital, and they were provided with a script to follow to introduce the study to the participant and ask them if they would like to take part in the first phase to screen for eligibility (Appendix A). If the patient was interested in participating, they entered eligibility phase of the study by
completing the RSS. The gatekeeper sent the first Participant Information Leaflet (PIL) (Appendix B), first Consent form (Appendix C) and a copy of the RSS to them via email or post. The gatekeeper kept a written record of the number of patients contacted. The participant was advised to read the PIL and if they agreed to participate they read and signed the consent form and completed the baseline RSS. The consent form was either posted or scanned in and emailed back to the PI. Participants could complete the RSS electronically using Qualtrics. They also had the option of completing a paper version which was then returned via post or scanned to email. The option of posting versus email or electronic submission of the RSS was done to avoid excluding any participants who may not have access to or be comfortable using emails or computer technology. Each participant was allocated an identification (ID) number at the outset of the eligibility stage. Participants who were eligible for the full trial would continue to use this ID number for the duration of the study when completing the weekly RSS. Once the completed consent form and RSS were received, the PI reviewed them to see if a score of >13 on the RSS was obtained. If this score was not obtained, the participant was advised that they had not met the study criteria and were advised to await their initial SLT assessment. If the participant achieved a score of >13 on the RSS, the PI then contacted the participant to review the study eligibility criteria with them. Participants needed to meet all the study criteria, obtain a score of >13 on the RSS and consent to participate in the full trial. If the participant satisfied all these criteria, the PI then provided information on the full trial procedure and sent them the second PIL (Appendix D). They were advised to read the second PIL and sign the second consent form (Appendix E). Participants were given up to three days to review the second PIL and decide whether they were happy to participate in the full trial. If they were, the second consent form was signed, and sent back to the PI via email or post.
2.5 Full pilot trial phase
Following recruitment to the full trial, participants were then randomly allocated to either the treatment or the control group via computer generation. The participants were then given specific instructions on what they needed to do depending on which group they were assigned to. At this stage the participant’s ENT consultant or GP was sent a letter updating them of their patient’s involvement in the study, as they have overall medical management of the patient (Appendix J). The participants in the control group did not receive treatment and were not advised to change anything that they were doing. They were informed that they met the inclusion criteria and had symptoms of LPR based on the RSS. They were informed that any necessary treatment plan would be discussed based on their full initial SLT assessment, as is usual care. While the control participants were not given any advice on treatment of their LPR, it was not possible to monitor whether participants carried out their own research. This approach is standard practice and did not place them at a disadvantage by being in the control group.
2.5.1 Treatment protocol
The current study adopted the same intervention protocol as McGlashan et al. (2009) of 10mls of Gaviscon Advance taken four times daily. Participants in the treatment group were advised to take 10ml Gaviscon Advance after each meal (breakfast, lunch and dinner) and once again before bed. They were advised to purchase a bottle of Gaviscon Advance from their pharmacy, read the enclosed Gaviscon Advance information leaflet and begin to commence the Gaviscon Advance protocol of 10mls 4 times daily the following day. Participants were advised in the second PIL that they would be expected to cover the cost of the Gaviscon Advance for the duration of the study, as is standard practice in clinical settings.

2.5.2 Reflux Symptom Score
Careful consideration was given to choosing the appropriate outcome measure tool for this study. The Reflux Symptom Index (RSI) is a 9-item questionnaire which has been standardised as a self-assessment tool in this population (Belafsky et al., 2002). The RSI is usually accompanied by physical signs seen in endoscopy and rated with the Reflux Finding Score (RFS) (Belafsky et al., 2001). However, the reliability and validity of the RFS have been questioned (Vance et al., 2020) and it is not commonly used in clinical practice amongst ENT consultants referring to this SLT service. Recently, it has been suggested that the RSI may not be robust enough to account for all the possible symptoms of LPR (Lechien, Bobin, Muls et al., 2020). The Reflux Symptom Score (RSS) was created following the World ENT Congress of the International Federation Otorhinolaryngological Society in Paris in 2016 (Appendix F). The authors reviewed the available self-rated tools and found none considered all of the possible symptoms that could be attributed to LPR. Therefore, the Society developed the 22-item RSS to be more detailed and robust in capturing all the possible symptoms of LPR based on expert opinion and the literature (Lechien, Bobin, Muls et al., 2019). In this newly developed tool, sections were included on GERD symptoms as well as respiratory symptoms which can often be associated with LPR. The authors found that a score >13 on the RSS was suggestive of LPR with a sensitivity of 94.5 and specificity of 81.0 in a cohort of 113 patients with LPR and 80 asymptomatic controls using receiver operating characteristic analysis. The authors concluded that these findings correlated with the RSI scores (Spearman’s \( \rho = 0.831 \)). While the French version of the RSS has been validated, it has been translated but not yet validated in English. Despite English-language validation, the test properties indicated that it is more sensitive in capturing changes amongst patients with LPR and would yield more detailed and robust findings amongst participants for this study in comparison to the RSI.

Both the treatment and the control group were asked to complete the RSS at weekly intervals for between 1-8 weeks. Participants in both groups were given weekly reminders to complete the
RSS. Reminders were done over the phone or via email either a day in advance or on the day that they had to complete the questionnaire. These completed questionnaires were then sent to the PI immediately to ensure accurate weekly intervals were kept. Participants that completed the RSS electronically were able to send their completed questionnaire almost instantaneously. Particular attention was given to reminding participants who were completing a paper copy of the RSS and emailing or posting it back to the PI. It was anticipated that these methods could result in a time delay, so every effort was made to avoid this. Participants in the treatment group were also reminded at these weekly intervals to ensure they took the appropriate amount of Gaviscon Advance and at the appropriate times.

2.5.3 Dependent and independent variables

Experimental studies explore causality between dependent and independent variables (Bowling, 2014). The independent variable in the definitive RCT is 10mls Gaviscon Advance taken 4 times daily. The dependent variables are the results of the self-rated Reflux Symptom Score at weekly intervals up to a maximum of 8 weeks (Table 2.2).

Table 2.2: Independent and dependent variables

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Dependent Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaviscon Advance 10mls taken 4 times daily versus no treatment</td>
<td>Self-rated Reflux Symptom Score at 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks</td>
</tr>
</tbody>
</table>

The feasibility of carrying out the definitive RCT was explored in this pilot trial. This procedure is outlined in Figure 2.3. The outcomes related to this trial’s research aims were reported using descriptive statistics as well as narratively. A research diary was kept to record any unforeseen circumstances that acted as barriers or facilitators to the study. This data was later extracted for analysis.
2.5.4 Study validity, reliability and fidelity

Internal validity is the extent to which the study design and implementation eliminate the possibility of bias (Moher et al., 2012). It can also be described as the extent to which observed treatment effects can actually be attributed to the differences in treatment and not confounding factors (Sedgwick, 2014). Internal validity was considered in this study by ensuring random allocation of participants which is a powerful tool for controlling threats to validity (Fraenkel et
al., 2012). Having a control group was also important in ensuring internal validity. The study inclusion/exclusion criteria used also minimised confounding factors. However, there were certain factors that were not controlled for and could impact on the internal validity of the study. It was not possible to use a placebo treatment option as there was none readily available. As a result, it was not possible to carry out study blinding. This could potentially result in ascertainment bias which is a distortion of the results of the outcome measures used because researchers and participants are aware of the treatment allocation (Moher et al., 2012). In addition, study location or time of day was not controlled for. Effort was made to ensure the outcome measure was completed weekly on the same day to ensure accurate measurement. Participants were phoned or emailed on the day they had to complete it. This pilot study allowed for a review of study procedures ahead of completing the full RCT. This would further enhance study validity in ensuring appropriate and optimal study design.

External validity is the extent to which the findings of the study can be generalised to other contexts (Moher et al., 2012). In this study, participants were recruited from one outpatient SLT setting via convenience sampling which may not be entirely representative of all people presenting with LPR symptoms. This is a private healthcare setting so people accessing this service are likely from a similar socioeconomic background.

Reliability relates to the consistency of measurements across different circumstances (Roberts & Priest, 2006). Lechien et al. (2020) found high internal consistency reliability (α = 0.969) and test-retest reliability (Spearman’s ρ = 0.92) which indicates excellent reliability of the RSS. However, participants in this pilot trial will complete the RSS at weekly intervals which is acknowledged to be slightly different to the validation study by Lechien et al. (2020).

Treatment fidelity refers to the strategies deployed to optimise the validity and reliability of behavioural interventions (Bellg et al., 2004). In this pilot trial, careful attention to study procedures as well as instructions to participants was done to ensure study fidelity. Verbal and written information and instructions given to both groups were kept as similar as possible (Appendix G).

2.5.6 Bias

To reduce selection bias and ensure the study is of high quality, proper randomisation of participants was crucial (Moher et al., 2012). The first step of randomisation is to generate an unpredictable allocation sequence to either the treatment or the “no treatment” control group. In this study, allocation was done using Excel computer generation by the PI. A random sequence was generated and saved in a separate Excel file. The second step of successful randomisation is
to conceal this sequence from investigators who are enrolling participants. In this study, administrative staff acted as gatekeepers when enrolling participants and they had no access to this allocation sequence. Once participants were recruited, the PI then assigned them to either the treatment or the “no treatment” no control group based on the allocation sequence. The order in which participants were contacted by the gatekeeper was not predictable or known to the PI in advance of them being recruited. Study blinding is an important method of minimizing bias as well but it was not possible in the current study due to lack of available placebo intervention to Gaviscon Advance.

2.6 Study Data

2.6.1 Data management
Careful measures were taken to ensure patient confidentiality by using participant identification numbers to store patient consent forms and RSS forms and by storing these documents on the password protected hospital drive. The data that was collected was inputted on a password protected Excel spreadsheet and saved on the secure hospital drive. This information included the participant’s ID number, name, age, gender, contact details, hospital medical record number, ENT diagnosis and results of the weekly RSS. A participant’s ID number was saved on a master code sheet which was password protected, encrypted and saved in the hospital shared drive. Only fully coded data was saved to Trinity College Dublin (TCD) One Drive account, which was also encrypted and password protected. Once data were collected, if no changes were made to the RCT protocol then this participant data would be included in the full RCT data. However, if changes needed to be made this data would be excluded from full RCT data analysis.

A data protection impact assessment was completed which deemed a rare or remote likelihood of risk to the data being that were being processed. The General Data Protection Regulation (GDPR), European Union (EU) 2016/679 (Citizens Information, 2018) governs all data processed in the hospital, so this also ensured that the privacy of the participants was upheld.

2.6.2 Data analysis
This pilot trial aimed to explore study design, recruitment, adherence to the intervention protocol and explore the outcome measure tool used (Table 2.3). The feasibility outcomes related to this aim were reported using descriptive statistics as well as narratively. A research diary was kept to record any unforeseen circumstances that acted as barriers or facilitators to the study. This data was later extracted for analysis. If elements of the procedures needed to be re-designed this could be done before conducting the full RCT.
Table 2.3: Research aims and analysis

<table>
<thead>
<tr>
<th>Research Aim</th>
<th>Analysis method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. To investigate the study design with regards to length of time participants were recruited for (1-8 weeks) and the feasibility of waitlist study design.</td>
<td>Review participant information with regards length of time they participated in the study by collating RSS scores and noting initial SLT assessment date. Data will be reported descriptively.</td>
</tr>
<tr>
<td>2. To explore how many eligible patients referred to the outpatient SLT service were enrolled in the study during the 3-month pilot time frame.</td>
<td>Gatekeepers will keep a record of people contacted and recruited and results will be collated by PI.</td>
</tr>
<tr>
<td>3. To determine whether the eligibility criteria used for participants were too broad or too narrow by reviewing recruitment rate.</td>
<td>Review the number of participants who were excluded and the reasons for this. This will be done descriptively.</td>
</tr>
<tr>
<td>4. To investigate adherence to the research protocol for both the treatment and control groups and in completing the weekly RSS.</td>
<td>Explore adherence to Gaviscon Advance protocol based on RSS and communication with participants via weekly reminders. Relevant data will also be extracted from the research diary Examine adherence to the RSS in terms of completion of the forms and sending them back in a prompt manner.</td>
</tr>
<tr>
<td>5. To catalogue any unforeseen circumstances that act as barriers or facilitators to this research in terms of study design, recruitment or analysis.</td>
<td>Data will be extracted from the research diary and reported narratively.</td>
</tr>
</tbody>
</table>

The primary research aim of the definitive RCT will be to explore how long participants needed to take Gaviscon Advance in order to notice clinically significant improvements in their LPR symptoms, as measured on the self-rated RSS. Achievement of a clinically significant difference is when scores on RSS fell to ≤13. This question could be answered with descriptive statistics alone. In order to determine whether further improvements can be obtained once a person reaches a score of 13, the RCT will examine whether the RSS scores continued to drop over the following weeks and whether this is statistically significant. A repeated measures ANOVA will be used to answer this research question. The final aim will be to compare the treatment and control groups and to see at which week the scores on the RSS become statistically significantly different. The average scores for both groups will be taken for each week and compared using a T-test. SPSS software will be used to carry out the inferential statistical analyses.
2.7 Ethical considerations

Ethical approval was sought from both the academic and hospital sites (see Appendix H and Appendix I). Ethical approval ensured that the principals of autonomy, non-maleficence, beneficence and justice were considered and maintained.

2.7.1 Autonomy and justice

Although participants in the study had some form of voice difficulties, this did not diminish their ability to provide informed consent, nor did they face any additional discomfort by having to use their voice for the purpose of the study. Participants were excluded if they had a clinically significant neurological illness which would impact their ability to consent and complete the weekly RSS questionnaire. Thus, participant’s autonomy was being considered and respected. For both groups, their RSS scores were recorded in the hospital medical records and would be available to their SLT to assist with their management. In addition, careful measures were taken to ensure patient confidentiality by using participant identification numbers to store patient consent forms and RSS forms and by storing these documents on the password protected hospital drive. This ensured that the privacy of the participants was upheld. As participants were randomly allocated in to either group this ensured that all participants were treated fairly.

2.7.2 Non-maleficence

It was suggested by the hospital Research Ethics Committee (REC) to inform each participant’s ENT or GP of their participation in the study, as they have overall management of the patient (Appendix J). The possible side effects of Gaviscon Advance needed to be considered for any unforeseen adverse effects. Participants in the treatment group were fully informed of possible side effects of taking Gaviscon Advance by being advised to read the detailed PIL and the accompanying leaflet when they purchased the bottle.

2.7.3 Beneficence

Participants in the treatment group were offered treatment before their initial SLT assessment so there was a benefit for this group pertaining to the ethical principal of beneficence. Although the control group did not receive the Gaviscon Advance treatment, they were not at any disadvantage as it is standard practice to await a full initial SLT assessment before management recommendations are provided. These participants received information on Gaviscon Advance following this initial assessment, as per usual care.
2.8 Summary
This chapter outlined the methodology chosen to answer the proposed research questions. The following chapter presents the results of this research study.
3. Results

3.1 Introduction
The aim of this pilot trial was to explore the feasibility of a definitive RCT to examine the effect of Gaviscon Advance on LPR symptoms in adults referred to an outpatient SLT service. In particular, the trial aimed to explore study design, recruitment, adherence to the intervention protocol and any other unforeseen circumstances that may impact on the study process.

3.2 Summary
This randomised pilot trial recruited four participants. Although only four participants were recruited, useful findings were still yielded in exploring these research aims. The key findings demonstrate that the definitive RCT is feasible, with a few suggested amendments.

3.3 Study design

3.3.1 Ethical approval
Recruitment could not commence until ethical approval was obtained. RECs ensure that studies being conducted with human participants comply with ethical principles (Das & Silva, 2017). Ethical approval had to be sought from both the outpatient hospital site REC as well as from the academic institute’s REC. The ethics application process proved to be lengthier than expected. The forms were first started in February 2020, just as the COVID-19 pandemic began. Careful considerations had to be given to the study design to navigate the constantly evolving guidelines and advice from both sites with regards to studies with participants. The application process was commenced in February 2020 with full approval being granted from both sites by the 21st October 2020.

Table 3.1: Timeline for full ethical approval from both RECs

<table>
<thead>
<tr>
<th></th>
<th>Academic REC approval</th>
<th>Hospital REC approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submission date</td>
<td>5th May 2020</td>
<td>24th July 2020</td>
</tr>
<tr>
<td>Revisions made</td>
<td>26th May 2020</td>
<td>29th September 2020</td>
</tr>
<tr>
<td>Full approval</td>
<td>2nd July 2020</td>
<td>13th October 2020</td>
</tr>
<tr>
<td>Full approval with amendments</td>
<td>21st October 2020</td>
<td>NA</td>
</tr>
</tbody>
</table>

Full approval was first granted by the academic REC. The hospital site’s REC subsequently advised that consent needed to be sought for participants to complete the RSS in order to be screened for eligibility for the full pilot trial. The rationale was that usual practice for patients awaiting their SLT assessment does not involve asking them to complete the RSS, therefore consent for this step must be sought. Those patients that verbally consented to complete the RSS then had to read a PIL and sign a consent form before doing so. If they then satisfied the eligibility
criteria, they were provided with a second PIL and consent form to complete to participate in the full trial. This amendment then had to be made to the academic REC application.

3.3.2 Trial timeline
The study was designed as a waitlist study. Participants were invited to participate in the study while they waited for their SLT initial assessment. At the time that the study was designed in 2020 the typical waiting time for initial assessments was between 6-8 weeks. The study time frame fluctuated between 1-8 weeks to reflect this. However, all participants (n=4) in this pilot trial received their initial SLT assessment within 4 weeks, so the length of the study period was shorter than first anticipated. As a result of it being a waitlist study, n=3/14 (21%) participants screened for eligibility were unable to participate in the full trial as they had their initial SLT assessment appointment scheduled in the next week. Therefore, there was not sufficient time for them to participate in the study.

3.4 Recruitment
3.4.1 Participant response rate
A total of 25 suitable participants were referred to the outpatient SLT clinic from ENT consultants and were invited to participate in the study during the 3-month recruitment timeframe from January to March 2022. Of those invited, n=14/25 (66%) were interested in participating in the study. The other patients (n = 11) declined to participate in the study or else cancelled their referral for an SLT assessment altogether. Of those participants who provided reasons for declining to participate or withdrawing their referral, resolution of their symptoms or self-report that reflux was not a factor in their presentation were the reasons cited.

Of the 14 patients who consented to be screened for eligibility for the full pilot trial, ten were excluded for a variety of reasons. A total of four participants were recruited to the full trial phase. (Figure 3.1).
3.4.2 Participant demographics

All four participants recruited to the study were female. They had a variety of different ENT diagnoses from four different ENT consultants. They ranged in age from 48 to 72 with the median age of 49.5.

Table 3.2: Participant demographics

<table>
<thead>
<tr>
<th>ID</th>
<th>Gender</th>
<th>Age</th>
<th>ENT diagnosis</th>
<th>Baseline RSS</th>
<th>Participation time</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1002</td>
<td>Female</td>
<td>49</td>
<td>Muscle tension dysphonia</td>
<td>71</td>
<td>4 weeks</td>
<td>Treatment</td>
</tr>
<tr>
<td>1003</td>
<td>Female</td>
<td>50</td>
<td>Vocal cord bowing &amp; poor adduction</td>
<td>61</td>
<td>4 weeks</td>
<td>Control</td>
</tr>
<tr>
<td>1009</td>
<td>Female</td>
<td>72</td>
<td>Functional dysphonia</td>
<td>63</td>
<td>3 weeks</td>
<td>Control</td>
</tr>
<tr>
<td>1013</td>
<td>Female</td>
<td>48</td>
<td>Bilateral moderate vocal cord nodules and Reinke’s oedema</td>
<td>190</td>
<td>3 weeks</td>
<td>Treatment</td>
</tr>
</tbody>
</table>

Figure 3.1: Flowchart of participant recruitment
3.4.3 Eligibility criteria

Participants were excluded from the study if they did not satisfy the eligibility criteria (Table 2.1). Of the 10 participants excluded, 50% of these were because they did not satisfy these criteria (Figure 3.1). Three participants were taking a PPI. One participant had a diagnosis of irritable bowel disease. This was described as significant by the participant so she was excluded on that basis as it would be a contraindication should she be randomly assigned to the treatment group.

3.5 Adherence to protocol

3.5.1 Gaviscon Advance

Two participants were randomly assigned to the treatment group. Participant 1002 was unable to tolerate Gaviscon Advance. She strongly disliked the taste and texture and discontinued it after five days. The other participant randomised to the treatment group took part in the study for three weeks. She reported no change in her symptoms during this period while taking Gaviscon Advance. She was away on holidays for one week during this time but reported that she continued to take the Gaviscon Advance while abroad.

3.5.2 RSS completion

There was a total of 18 RSS forms completed by the four participants, which was a 100% success rate. Most of the RSS forms were completed accurately and in full (n=15/18; 83.3%). However, 3 sections were left blank by two participants (see Table 3.3). These omissions impacted on the overall RSS scores. Three participants opted to complete the RSS in paper version and post or email it back to the principal investigator. One person opted to complete it using interactive PDF and email it back. No one opted to complete it electronically via Qualtrics. For two participants, the PI printed out copies of the RSS and posted them out with stamped, addressed envelopes for them to be able to complete and post back at weekly intervals.

Table 3.3: Method of completion of RSS

<table>
<thead>
<tr>
<th>ID</th>
<th>RSS completed in full</th>
<th>Hard (paper) or soft (word/pdf) copies</th>
<th>Post or email</th>
<th>Other note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1002</td>
<td>Yes</td>
<td>Hard (printed by participant)</td>
<td>Email</td>
<td>Difficulty adding electronic signature to consent forms</td>
</tr>
<tr>
<td>1003</td>
<td>No – “Abdominal symptoms” incomplete week 3 and week 4.</td>
<td>Soft (PDF)</td>
<td>Email</td>
<td>Nil</td>
</tr>
<tr>
<td>1009</td>
<td>Yes</td>
<td>Hard (printed by gatekeeper &amp; PI)</td>
<td>Post</td>
<td>PI sent stamped, addressed envelopes</td>
</tr>
<tr>
<td>1013</td>
<td>No – “Respiratory symptoms” incomplete week 2</td>
<td>Hard (printed by gatekeeper &amp; PI)</td>
<td>Post</td>
<td>PI sent stamped, addressed envelopes</td>
</tr>
</tbody>
</table>
3.5.3 RSS scores

To calculate the overall score of the RSS, the “Frequency” is multiplied by the “Severity” for each symptom and added (Appendix F). The baseline RSS score for participants was between 61-190 with the average score of 96.25. Scores for participants in the control group did not remain stable. Participant 1003 had a marked increase in her RSS scores at week 3 and week 4. This coincided with her developing an upper respiratory tract infection (URTI). Participant 1009 had a slow increase in her RSS scores with a marked jump in her score at week 3 from 73 to 116, for reasons unknown. In the treatment group, there was no noticeable change in scores across the weeks of the study (Figure 3.2).

![RSS Scores graph](image)

**Figure 3.2:** Participants' RSS scores

At the end of the RSS form there is a question asking whether the participant thinks the tool assesses their current complaints. This was answered as “yes” in n=13/18 (72%) completed RSS forms. This question on the remaining three forms from one participant and two from one other participant were left blank. It was unclear why these two participants left this section blank at times. Both participants who did not complete the QOL impact section missed other sections on the forms as described previously.

3.6 Unforeseen circumstances

A study diary was kept to record notes on any unforeseen circumstances or events that arose during the pilot trial. Data was later extracted for analysis and is discussed below.
3.6.1 Staffing

Changes to staffing meant that the pilot trial was not fully established until January 2022 despite ethical approval since October 2020. There was one post either vacant or with reduced cover from November 2020 to February 2021. The PI was on leave from December 2020 to January 2022. There was re-distribution of staff during 2021 due to the COVID-19 pandemic which resulted in no allocated research time. The trial commenced in January 2022 once the PI returned to work which resulted in an overall delay for the research.

3.6.2 Gatekeeper

The study gatekeeper was initially planned to be one of the SLTs in the hospital. However, the service structure changed with patients being offered their initial appointments by outpatient hospital administrative staff instead of the SLTs. The administrative staff were not aware of the study so had to be informed about it, provided with the gatekeeper script (Appendix A) and to be agreeable to act as gatekeepers. There were already many demands on their time, so acting as study gatekeepers was an additional task for them. Three administrative staff were informed about the study. One administrator assumed the role of lead gatekeeper and handled all aspects of study recruitment. However, this staff member was re-deployed to a different area of the hospital and so different staff members of the administrative team then shared the role of gatekeeper. The PI had to be in regular contact with the gatekeepers to encourage recruitment of suitable patients, to problem solve any issues that arose, to remind staff members to follow up with participants if they had not had an opportunity to contact them and to ask for updates on how recruitment to the eligibility phase was progressing. This resulted in a lag in recruitment time. In particular, there were no participants recruited for a 5-week period which coincided with the key gatekeeper being re-deployed. Additional time had to be allocated by the PI to ensure gatekeepers were supported and guided in their role in the study.

3.6.3 Documentation

Some participants found it challenging to complete the documentation and send it back to the PI. This was for a variety of reasons. Several of the participants did not have access to a printer to be able to print the emailed documents. Other times, those that did manage to print out the documents then did not have access to or were unable to use a scanner to email them back and did not want to post them. One participant sent in photographs of her completed forms via email. Although not suggested, one participant chose to complete her forms electronically using interactive PDF. One patient tried to send her completed forms back via Google Drive which was not compatible with hospital computers. As these were not suggested methods of completing and sending documents, the PI had to contact the participants to reiterate how to send the documents back. This resulted in delays to recruitment to both stages, for one participant in particular (1002). As a result of these issues, two participants were sent out the PILs, consent forms and appropriate number of copies of the RSS with the dates to be completed on them. Stamped, addressed envelopes were also provided. It was originally anticipated that it would take approximately 2-3 days from being contacted by the gatekeeper to the PI receiving the first consent form and baseline
RSS. However, results showed that this took between 2-10 days. It was also anticipated that the time to complete the second consent form and be screened for eligibility to the full trial would take another 2-3 days. This timeframe varied from between 1-8 days (Figure 3.3).

![Recruitment time in days for each participant]

**Figure 3.3:** Recruitment time in days for each participant

### 3.6.4 Participant factors

Participant 1013 was on holidays for one week during the study so therefore was not contactable for the weekly reminder. She advised the PI that she would continue taking the Gaviscon Advance and complete the RSS while away. She also reported a lot of voice use on this holiday with overall deterioration in her vocal symptoms as a result. Participant 1003 became unwell with a sinus and throat infection during the study, so this impacted on her symptoms and RSS results.

### 3.7 Summary

The above results highlight that the definitive RCT is feasible. However, some issues arose that were both expected and unforeseen. The following chapter discusses the results and provides suggested amendments for the definitive RCT.
4. Discussion

4.1 Main findings
In this pilot trial, the results showed that it would be feasible to conduct a definitive RCT to explore the effect of Gaviscon Advance on LPR symptoms in adults attending an outpatient SLT service. The following chapter explores the results with regards to study design, recruitment, adherence to the study protocol and any unforeseen circumstances and makes suggested amendments for the definitive RCT.

4.2 Interpretation of main findings

4.2.1 Study design
Research Ethics Committee approval took significant longer than expected, both due to the COVID-19 pandemic and request to include a two-stage consent process. The CONSORT guidelines for RCTs also suggest the first phase to be eligibility screening followed by randomisation into the fully study (Moher et al., 2012). However, as there were to be two sets of PILs and consent forms before full recruitment to the study, additional time then had to be allocated for the recruitment phase of the study design. Based on this finding, it would be beneficial for researchers to allow sufficient time for ethical approval from two sites and if possible, to seek advice informally from REC before submitting the application particularly in the context of a global pandemic.

The waitlist study design was an appropriate one to choose. The literature suggests that it is more ethical to offer participants the treatment after a waiting period than to offer them a placebo control and that this waiting period does not appear to cause any significant deterioration in symptoms (Elliott & Brown, 2002). Participants in this setting were waiting for several weeks for their initial SLT assessment, as is standard practice. They had not had any other SLT input, which helped to avoid confounding factors. However, participants were informed that they met the criteria for LPR so may be inclined to research management of this themselves. The definitive RCT should reinforce instructions to participants in both groups not to modify their diet or lifestyle factors whilst participating in the research.

This pilot trial indicated that it would be unlikely to recruit participants to the study at weeks 6, 7 and 8. The outpatient service capacity had increased since the study was first designed so patients were being offered initial assessments sooner and thus, the length of time available for them to participate in the trial was shorter than first predicted. It would be prudent to consider reducing the length of the study to a 1-6 week study to reflect this. This is a more realistic timeframe in
which to recruit participants and will still provide useful data, as often patients can notice improvements in their symptoms in a matter of weeks and research suggests that treatment response at 6 weeks is indicative of longer-term response (Lechien, Saussez et al., 2022).

### 4.2.2 Participant response rate

Twenty-five patients were contacted to be invited to participate in the eligibility phase by the study gatekeepers during the 3-month pilot trial timeframe. This was lower than anticipated. This may have been due to the fact that a large proportion of referrals to the outpatient service during this time were for communication and swallowing assessments, as opposed to voice assessments. This was also as a result of the exclusion criteria as patients would not have been invited to participate if there was some information on their referral that would have excluded them e.g. taking a PPI. Of these 25 patients, 66% agreed to participate in the eligibility phase (n=14/25). Interestingly, only 14% (n =2/14) were ineligible due to RSS<13, indicating a high prevalence of LPR among those recruited.

Ensuring enough participants are recruited to a research study is vital to its success, yet often researchers fail to do this. Response rate in RCTs has been highlighted as an issue in the literature, with only 55% of RCTs recruiting to within 80% of their sample size target (Walters et al., 2017). This result is in keeping with the literature and shows that recruitment of participants can often take longer than expected. Strategies have been suggested to facilitate recruitment which include carrying out telephone reminders and choosing open, unblinded designs (Treweek et al., 2010). In this trial, email or telephone reminders were carried out weekly and an unblinded study design was chosen. This is also valuable information when determining the sample size calculation for the definitive RCT. Oversampling at the outset of recruitment could offset study attrition at the latter weeks. Avoiding attrition in RCTs is important to avoid bias as it may result in different characteristics of participants between the two randomised groups (Dumville et al., 2006).

### 4.2.3 Eligibility criteria

As a result of the chosen eligibility criteria, 35% of those participants who wanted to participate and who scored above 13 in the RSS were excluded (n=5/14). This was done to avoid for confounding factors on study outcomes, which is an important part of RCTs. However, most of these excluded participants may still be recommended to take Gaviscon Advance based on their SLT assessment. In clinical practice, Gaviscon Advance could still be recommended for a patient even if they smoked, had recently had a URTI or were taking a PPI. While RCTs provide important information, at times their applicability to a clinical context may be limited due to the often-stringent eligibility criteria. Results of this trial highlight that these criteria were too stringent and resulted in some patients being excluded, who would not be excluded in usual
Clinical practice. In reviewing the CONSORT guidelines for reporting on pragmatic trials (Zwarenstein et al., 2008), it is advised that eligibility criteria do not need to be as stringent as traditional RCTs. Therefore, it would be worth reviewing the eligibility criteria for this RCT to ensure it is generalisable to the clinical context. To do this, the exclusion of participants if they smoked should be removed. While smoking may be associated with symptoms of LPR, it would be pragmatic to include smokers in the study to help increase the generalisability of the outcomes. In addition, people who had had a URTI in the past one month should not be excluded from the study. While symptoms of LPR can appear similar in smokers and people with URTIs, they can also appear similar to those caused by allergies, vocal abuse and inhaled environmental irritants (Lechien et al., 2018; Ah-See et al., 2012). It is not practical nor realistic to include all of these as exclusion criteria as it would greatly impact on recruitment and generalisability of the trial outcomes. Instead, the definitive RCT could carry out subgroup analyses for smokers versus non-smokers and people with URTIs and those without to examine for significant differences in responses to Gaviscon Advance.

It is acknowledged that 50% of patients with LPR also have GERD (Lechien, Akst, Hamdan et al., 2019). Therefore, some people with LPR may notice improvement in their symptoms taking a PPI. For this reason, people taking a PPI should be continued to be excluded from this study as results could be impacted by the PPI rather than the study protocol.

4.2.4 Gaviscon Advance
There were two participants randomly assigned to the treatment group to take Gaviscon Advance. The first participant attempted to take it but strongly disliked the taste and texture and so had to discontinue it after only 5 days. The PI attempted to problem solve this with her and suggested trialling another flavour, but she declined. This protocol does require taking a large amount of Gaviscon Advance over the course of the study which may not be well tolerated across all participants. However, in clinical practice most patients tolerate the protocol well.

The second participant assigned to the treatment group participated for three weeks and found no change in her symptoms reported both verbally and reflected in her RSS scores. This may have been because she was only recruited in the study for three weeks. Most studies on the effectiveness of Gaviscon Advance look at treatment effects at 2 to 6-month time frames, so this might have been too short of a window to see treatment effects for this participant. Additionally, research suggests that for some people there can be a limited response to treatment, particularly for patients with more severe symptoms at the outset (Lechien, Saussez, Muls et al., 2021). This participant had a score of 190 on her baseline RSS which was the highest amongst participants. She was on
holidays for one week during the three-week period with increased demands on her voice but reported that she continued with the Gaviscon Advance protocol.

In reviewing the literature, adherence to and tolerance of Gaviscon Advance was not something that was reported on in other similar studies (McGlashan et al., 2009; Wilkie et al., 2018). In general, low levels of adherence has been reported in clinical trials with between 25 -50% of participants not adherent (Robiner, 2005). Strategies to promote adherence include pre-randomisation screening and adherence enhancement behaviours such as pre-trial education, reminders to participants and simplifying information provided to participants (Robiner, 2005). The definitive RCT should ensure sufficient education is provided to participants during the recruitment process with written PILs and during the phonecalls with the PI to promote adherence to Gaviscon Advance.

4.2.5 Adherence to RSS
In general, there was good adherence to completing the RSS. While weekly reminders were sent, the PI could not ensure the RSS was completed on the exact required day as participants completed them in a place convenient for them. At times, certain sections of the RSS were not completed for reasons unclear. This impacted on the overall score of the RSS. The RSS has been reported to be somewhat lengthy and burdensome to patients in clinical practice (Lechien, Bobin et al., 2020). Ensuring adherence to and completion of study tools is vital in research. If study protocols are incomplete, this could contribute to statistical variance and erroneous conclusions being drawn (Robiner, 2005). The literature highlights the importance of effective communication with participants to highlight the importance of adherence and encourages “adherence-promoting” interventions such as reminders and contingent reinforcement (Robiner, 2005, p. 69). Therefore, participants should be advised during the initial phone call from the PI that adherence is key and that all questions on the RSS need to be completed. The PI should discuss with each participant the easiest method for them to complete the RSS, either hard copies posted out or by completing it electronically via Qualtrics. They should be advised during their weekly reminders to complete every section on the RSS. If any forms are returned incomplete, the PI should follow up with the participant and ensure any missing sections are completed.

Although not included in the total RSS score, the “QOL score” was left blank by 2 participants on each RSS form they completed. The exact reason is unclear, but it may be that they did not understand what this section was referring to. All participants opted to complete the RSS in paper form or on PDF/Word documents and post or email it back to the PI. Interestingly, one person completed it via interactive PDF, which wasn’t an option considered initially but was most convenient for her. No one opted to complete the RSS electronically using Qualtrics. This may
reflect participants level of comfort with completing online tools and preference for paper or PDF/Word copies.

### 4.2.6 Unforeseen circumstances: Staffing, documentation, communication & participant factors

Due to staffing shortages and the PI going on leave for 12 months, the study was paused and recruitment postponed. There was no other staff member available to set up and run the study. This reflects the reality of a busy clinical setting with often unavoidable changes to staffing and resources.

Another method to encourage recruitment is to reduce participant burden (Newington & Metcalfe, 2014). In this trial, participants were required to read two PILs, read and sign two consent forms, complete a baseline 22-item RSS and weekly RSS forms. There is a lot of paperwork in this, so the PI must attempt to make this process as easy for participants as possible. Some participants had difficulty completing the forms if they were emailed out to them. This was due to lack of access to a printer or challenges with signing the consent form and completing the RSS on their computers. Results showed that this could result in delays to recruitment. In addition, it increased burden on the participant trying to problem solve or having to repeat their attempts again. In the definitive RCT, gatekeepers and the PI should offer to print out the information and post it to the participants along with a stamped, address envelope to return the signed consent and completed RSS forms in. This would reduce participant burden and ensure forms were returned in a timely manner.

Research has shown that it is common for there to be challenges when recruiting through gatekeepers, particularly in gaining initial access to participants (Spacey et al., 2021). This is reflected in the current pilot trial. While gatekeepers involved in this trial were very keen to facilitate recruitment, they had a lot of demands on their time in their already busy day. One member of the administrative team took the lead on recruitment initially. Research suggests that key gatekeepers should be identified early on and that attention is focused on gaining their support (Mc Fayden & Rankin, 2016). However, when this staff member left this role there was no other key gatekeeper identified. This period coincided with no participants being recruited to the study for 5 weeks. It is also important to ensure clear information is shared with gatekeepers and to encourage gatekeepers to feel motivated about the research (Mc Fayden & Rankin, 2016). This could be achieved by identifying a key gatekeeper and having a short weekly face-to-face update meeting with gatekeepers to ensure a seamless process for staff and participants in recruitment to the eligibility phase of the study.
4.3 Summary of amendments for definitive RCT

The results of this pilot trial show that the definitive RCT is feasible with some amendments to consider (Figure 4.1). Reducing the length of time of the study to 1-6 weeks is more realistic as patients are being offered earlier initial assessments and no one is likely to be recruited in the study for longer than 6 weeks. The potential drawback of this timeframe could mean that less participants are recruited at the latter weeks, which must be considered when determining the full RCT sample size. With regards study eligibility, it was originally decided to use stringent criteria similar to McGlashan et al. (2009) to help reduce any confounding factors on study outcomes. However, results show that these criteria meant 35% of recruited participants were not eligible to participate in the full trial. The CONSORT guidelines for pragmatic RCTs suggest that eligibility criteria do not need to be too stringent, as the goal of the RCT is to guide clinical practice (Zwarenstein et al., 2008). While care must be taken not to have eligibility criteria too broad, it would be worth removing the exclusion criteria of having had a URTI in the past one month and smoking, to encourage generalisability of study findings.

Working closely with study gatekeepers is important. A key gatekeeper must be identified and if this person changes roles, then a new person should be appointed. A short weekly meeting would help to ensure participants are being contacted, recruitment is ongoing and that gatekeepers feel supported in their role in the study.

Participants should be posted out their PIL and consent forms by the gatekeeper for the eligibility phase. They will also be posted out their second PIL and consent form by the PI if eligible to participate in the full study. They will be provided with stamped addressed envelopes in which to return the signed forms in. With regards to the RSS, they will be posted out a copy along with their initial PIL and consent form by the gatekeeper. If they progress to the full study, the PI will offer to either send out copies of the RSS with stamped addressed envelopes for the weeks that they are involved in the study or else they will be sent a link to complete the RSS electronically via Qualtrics. The PI will also discuss with participants at this point about how to complete the RSS in full and explain each section. Nothing will need to be printed out by the participant or completed on word or PDF. This should encourage more streamlined completion of documentation to reduce participant burden and ensure timely recruitment to the study phases.
4.4 Limitations

This pilot trial explored the feasibility of a full pragmatic RCT with regards to study design recruitment, adherence to study protocol as well as any unforeseen issues that may arise. While this is a comprehensive exploration of the study, it is not exhaustive and so, there may still be some remaining uncertainty about study feasibility. It remains unclear whether there will be enough participants recruited at latter weeks of the study. There may be further unforeseen circumstances such as staffing or resource changes which will have to be problem-solved during the study. However, results of the pilot trial will enable the PI to put measures in place regarding
study documentation and communication to attempt to mitigate any potential future issues in these areas. There was a time constraint on this pilot trial which impacted on the number of participants recruited. While this was a limitation of the current trial, results still provided sufficient information be able to examine the feasibility of the full RCT.

Assessment of LPR in this trial was done using the self-rated RSS. The results must be interpreted with this in mind. There may have been over-diagnosis based on the RSS alone, but as there are no other instrumental evaluation options in this setting it is the only available tool. In addition, the duration and severity of the participant’s dysphonia was not controlled for, so this may impact results and scores on the RSS. It could be helpful for future research to explore whether duration and severity of dysphonia impacted scores on the RSS. The RSS tool captures a QOL score for each component. Future studies could explore whether a reduction in LPR symptoms correlates with a reduction in the QOL impact for participants and if so, does this happen once overall RSS score falls below 13 or at a different time.

It was not possible to obtain a placebo version of Gaviscon Advance for this trial, so this may be a potential source of bias within the trial design. Care was taken to ensure randomisation of study participant by using a computer-generated randomisation sequence. However, it was not possible to blind the principal investigator to the allocation of participants, so care had to be taken not to allow for any subtle biases.

4.5 Future research

To facilitate recruitment and encourage generalisability of the findings, recruiting participants from other sites would be advantageous. This could lead to more robust findings. It would also be worth considering the possibility of a similar RCT but to recruit participants after they had their initial SLT assessment. All participants would undergo a full voice assessment and be provided with vocal hygiene and lifestyle advice. If they satisfied the eligibility criteria they could provide consent and be recruited to the full study. This would make it easier for gatekeepers to recruit participants and for documentation to be provided as it could be handed to them in person. Participants would then be randomly assigned to the treatment or control group for a set period, in contrast to the waitlist design where the length of participation time fluctuated. However, careful consideration would have to be given to the ethical factors in this design for those who were randomly assigned to the control group. These participants may not have any other treatment during this period apart from the vocal hygiene and lifestyle advice including dietary advice. They also pay a fee for this SLT service. So, the advantages of this study design would have to be carefully weighed against any potential disadvantages. Comparing the findings of a study like this with the findings of the current trial would show whether Gaviscon Advance in addition to these
other SLT recommendations would provide additional benefit compared to taking Gaviscon Advance in isolation.

4.6 Conclusions

Results of this pilot trial show that a definitive RCT exploring the effect of Gaviscon Advance on LPR symptoms in adults referred to an outpatient SLT service is possible. This RCT plans to explore the effects, at weekly intervals, of taking Gaviscon Advance four times daily for a period of up to 6 weeks. In doing this preliminary pilot trial, the study design, recruitment, adherence to the study protocol and unforeseen circumstances were reviewed. In general, this RCT is feasible with the following suggested amendments:

1. Reduce the time of study from 1-8 weeks to 1-6 weeks.
2. Provide study documentation either posted out or online via Qualtrics. Avoid emailing documentation as participants were unable to print or complete it electronically.
3. Identify one key gatekeeper and conduct weekly review meetings.
4. Allow longer time for study recruitment and ensure weekly reminders to participants.
5. Remove exclusion criteria of 1) having an upper respiratory tract infection in the past 1 month and 2) smoking.
Reference List


Appendices

Appendix A Gatekeeper script

A research study is being carried out by Kate Grehan, Senior Speech and Language Therapist. Any patient being referred to Speech and Language Therapy from an ENT consultant is being invited to participate.

The study is looking for patients that have silent reflux as part of their presentation of their voice problem. Silent reflux is a type of reflux that you usually do not feel but can cause or contribute to your voice problems. Kate will check if you have silent reflux by asking you to complete a questionnaire. If silent reflux is confirmed, you may be asked to take Gaviscon Advance for the weeks leading up to your initial SLT assessment.

Gaviscon Advance is a standard treatment option for patients with silent reflux. Participants will be randomly allocated into a Treatment group or a Control group. The Treatment group will be advised to take Gaviscon Advance daily until their appointment. The Control group will have no treatment while they wait for their appointment. Both groups will complete the questionnaire weekly until the time of their initial SLT appointment.

Would you be interested in participating in the study? If so, I will send you a Patient Information leaflet and the questionnaire the Reflux Symptom score over email now. The Reflux Symptom Score can be completed online or a hard copy and posted or emailed to Kate, whichever you prefer? I will post a Consent form along with your initial SLT appointment date. Kate will contact you later today or tomorrow once you’ve read the information leaflet and completed the questionnaire and consent form with more information on how to participate. I will give you a participant identification number for you to use to complete the Reflux Symptom Score questionnaires.
Appendix B 1st Participant Information Leaflet

Initial Patient Information Leaflet and Consent Form

Determining eligibility to participate in a randomised, controlled pilot trial on the effect of an over the counter medication on laryngopharyngeal reflux

Study Code (REC ref. No.): BEA0149
Protocol Version/date: 24th July 2020
Investigator Name: Kate Grehan, Senior Speech and Language Therapist, Beacon Hospital
Academic Supervisor: Dr. Ciarán Kenny, Clinical Speech and Language Studies, Trinity College Dublin
Data Controller’s/joint Controller’s Identity: Trinity College Dublin (for research data), Beacon Hospital Board (for hospital medical records)

Data Controller’s/joint Controller’s Contact Details: Clinical Speech and Language Studies, Trinity College Dublin, Dublin 2. Beacon Hospital, Sandyford, Dublin 18
Data Protection Officer: Mr John Eustace (Trinity College Dublin), Mr Brian Fitzgerald (Beacon Hospital)
DPO’s Contact Details: Mr John Eustace, Data Protection Officer, Secretary’s Office, Trinity College Dublin, Dublin 2.
Mr Brian Fitzgerald, Beacon Hospital, Sandyford, Dublin 18

Introduction and Background Information

What is the purpose of the study?
This is a short study that will determine your eligibility to participate in a larger study regarding an over-the-counter medication in the treatment of laryngopharyngeal reflux. Laryngopharyngeal reflux can be a cause of vocal symptoms in some people. If you are eligible to participate in the larger study, you will be provided with further information and randomly assigned to the treatment group or the control group, all while awaiting your initial Speech and Language Therapy assessment.

Who is organising the research?
This project is being carried out as part of a Voice Masters through the Clinical Speech & Language Therapy Department in Trinity College Dublin.

What will happen during the study?
You will be asked to read this form and if you consent, to sign the attached consent form and post or email it to the Principal Investigator Kate Grehan at The Physiotherapy Department, Suite 20, Beacon Hospital or Error! Hyperlink reference not valid.
You will also be asked to complete a 22-item questionnaire called the Reflux Symptom Score. This can be done electronically or on paper and posted or emailed to Kate Grehan. Kate will contact you to discuss your results in the questionnaire and if you are presenting with symptoms of laryngopharyngeal reflux, Kate will review the study inclusion and exclusion criteria with you and provide more information on the next stage of the study. Inclusion criteria are as follows: adults referred by an Ear, Nose and Throat (ENT) Surgeon, above 18 years who provide written consent to partake in the study with a score above the cut off in the Reflux Symptom Score. Participants will be excluded if they smoke, have a clinically significant neurological illness (this includes people with a cognitive impairment, diagnosis of Dementia or any person that may find it challenging to complete the weekly questionnaires as a result of a neurological illness), significant gastrointestinal illness, have had an upper...
respiratory tract infection in the past 1 month, are currently using anti-reflux medication (e.g. proton pump inhibitor, alginate), have a significant dysphagia (swallowing problem), are on a salt restricted diet or are undergoing any other medical investigations/treatment for their symptoms. The above criteria will be reviewed through discussion between the Principal Investigator and the patient, as well as from the medical history from the ENT referral letter or Beacon Hospital records.

**How many people will take part in the study?**

We are aiming to recruit over 84 participants for this study.

**What do I have to do?**

Read this Participant Information Leaflet and if you would like to proceed, you can sign the attached Consent Form and email or post it to Kate. In addition, you should complete the Reflux Symptom Score electronically or a paper version and email or post this to Kate. Kate will contact you over the phone within 1-2 days to review the results and see if you are eligible to participate in the next stage of the study.

**How long will I be on the study?**

If you consent, you will be advised to read the Participant Information Leaflet, complete and post or email the Consent Form and Reflux Symptom Score to Kate. Kate will then contact you over the phone to review your eligibility. This will take 1-2 days. If you do not meet the study criteria based on the information you provide, your participation in the study will stop here, and you will attend for your initial Speech and Language Therapy appointment. If you do meet the study criteria, you will be provided with more information on the next stage of the study which will take place while you are waiting for your initial Speech and Language Therapy assessment (maximum 8 weeks).

**Do I have to take part?**

No, it is up to you to decide whether or not to take part. If you do decide to take part, you will be asked to sign the attached consent form and keep a copy of this information leaflet. If you decide to take part but later change your mind, you are free to withdraw at any time without giving a reason. This will not affect the standard of care you receive. Likewise, your Primary Investigator Kate Grehan may decide to withdraw you from the trial if it is in your best interest.

**What are the alternatives for treatment?**

If you decide not to participate, you will just wait for your initial Speech and Language Therapy assessment as is standard practice.

**What are the possible risks/side effects of participating in this study?**

There is no associated risk in reading the Information Leaflet and completing the Consent Form and Reflux Symptom Score. Should you progress to the next stage of the study, any potential risks with the over-the-counter medication will be discussed at that time.

**What are the possible benefits from taking part in this study?**

Completing the Reflux Symptom Score is a tool to facilitate assessing for the presence of laryngopharyngeal reflux, which will help in your overall management of your vocal symptoms.
Can I stop being in the study?
Yes, you can decide to stop at any time. This will not affect the standard of care you receive.

Can anyone else stop me from being in the study?
The study Principal Investigator may stop you from taking part in this study at any time if:
- It is in the best interest for your health
- You do not follow your responsibilities for taking part in the study
- It is discovered at a later time that you do not meet the study participation requirements
- You need treatment not allowed in the study
- Administrative reasons require your withdrawal

What happens if I am injured because I took part in this study?
There is no anticipated injury risk from reading and completing the forms.

Will my taking part in this study be kept confidential?
Your privacy is important to us. We take many steps to make sure that we protect your confidentiality and keep your data safe. The personal data that we collect about you for the purpose of the research study will be kept strictly confidential. You will be provided with a participant Identification (ID) number. This ID number will be used to store your Consent Form and Reflux Symptom Score form. These forms will be kept in a password protected folder which will be saved on Beacon UCD Academy drive. The Principal Investigator Kate Grehan will have access to this folder. If the Principal Investigator is not available, two research assistants (both Senior Speech and Language Therapists) will have access to this folder. If you do not meet the criteria to proceed to the larger stage of the study, your Consent Form will be destroyed and Reflux Symptom Score results will be saved to your Beacon Hospital record system Meditech, as it will be relevant to your Speech and Language Therapy management. If you do meet the criteria to participate in the larger study, you will be provided with more information on how your future data will be stored.

You are entitled to:
- The right to access your data and receive a copy of it
- The right to have your data transferred to another organisation or “data controller”
- The right to restrict or object to processing of your data
- The right to object to any further processing of the information we hold about you (except where it is de-identified)
- The right to have inaccurate information about you corrected or deleted
- The right to request deletion of your data

By law you can exercise these rights in relation to your personal data, unless the request would make it impossible or very difficult to conduct the research. You can exercise these rights by contacting Trinity College Data Protection Officer, Secretary’s Office, Trinity College Dublin, dataprotection@tcd.ie.

What are the costs of taking part in this study?
There are minimal costs involved in taking this study. If you decide to print and/or post forms for the purpose of this study, you will have to cover this cost. You will not be paid for your participation in this study.

Who has reviewed and approved this study?
This study has been reviewed and approved by Beacon Hospital Research Ethics Committee and Trinity College Research Ethics Committee.

If you have any concerns or questions you can contact:

1. Principal Investigator: Kate Grehan, Senior Speech and Language Therapist, Beacon Hospital on 01 2938699 or Error! Hyperlink reference not valid.
2. Research Supervisor: Dr Ciarán Kenny, Clinical Speech and Language Studies, Trinity College Dublin on Error! Hyperlink reference not valid.
3. Data Protection Officer, Trinity College Dublin: Data Protection Officer, Secretary’s Office, Trinity College Dublin, Dublin 2. Email: Error! Hyperlink reference not valid. Website: Error! Hyperlink reference not valid.
4. Mr Brian Fitzgerald, Data Protection Officer, Beacon Hospital, Sandyford, Dublin 18

Under GDPR, if you are not satisfied with how your data is being processed you have the right to lodge a complaint with the Office of the Data Protection Commission, 21 Fitzwilliam Square South, Dublin 2.
Appendix C 1st Consent form

Informed Consent Form (initial form)

Determining eligibility to participate in a randomised, controlled pilot trial on the
effect of an over the counter medication on laryngopharyngeal reflux

Primary Investigator Name: Kate Grehan  Hospital Name: Beacon Hospital

Please Initial box

1. I confirm that I have been given a copy of all 4 pages of the Patient Information Leaflet and Consent form. I have read the patient information leaflet and consent form or it has been read to me. This information was explained to me and my questions were answered.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my medical care or legal rights being affected.

3. I understand that relevant parts of my medical records may be seen by Kate Grehan, Senior Speech and Language Therapist, two research assistants Aimée Holden and Kerrie Mc Carthy, Senior Speech and Language Therapists.

4. I understand and give informed consent that data related to me collected during this study will be processed and analysed as is required by this clinical study and according to the Data Protection Act.

5. I understand that my data may be used for research as described in the Patient Information Leaflet.

6. I voluntarily agree to take part in this study having been fully informed of the risks, benefits and alternatives.

Please initial the appropriate box:
- I agree that my data be processed for the purpose of this study and retained for use in the next stage of the study, should I be eligible to participate
- I DO NOT AGREE that my data may be kept for use in the next stage of the research study
- I understand I will not be entitled to a share of any profits that may arise from the future use of my material/data or products derived from it.

_________________ ___________________ ____________
Name of Patient (Print)  Signature of Patient  Date

_________________ ___________________ ____________
Name of Investigator (Print)  Signature of Investigator  Date
Appendix D 2nd Participant Information Leaflet

Participant Information Leaflet and Consent Form

A pilot randomised trial on the effect of Gaviscon Advance on laryngopharyngeal reflux symptoms in adults referred to an outpatient Speech and Language Therapy service

Study Code (REC ref. No.): BEA0149
Protocol Version/date: 24th July 2020

Investigator Name: Kate Grehan, Senior Speech and Language Therapist, Beacon Hospital
Academic Supervisor: Dr. Ciarán Kenny, Clinical Speech and Language Studies, Trinity College Dublin
Data Controller’s/joint Controller’s Identity: Trinity College Dublin (for research data), Beacon Hospital Board (for hospital medical records)
Data Controller’s/joint Controller’s Contact Details: Clinical Speech and Language Studies, Trinity College Dublin, Dublin 2. Beacon Hospital, Sandyford, Dublin 18
Data Protection Officer: Mr John Eustace (Trinity College Dublin), Mr Brian Fitzgerald (Beacon Hospital)
DPO’s Contact Details: Mr John Eustace, Data Protection Officer, Secretary’s Office, Trinity College Dublin, Dublin 2. Mr Brian Fitzgerald, Beacon Hospital, Sandyford, Dublin 18

Introduction and Background Information

What is the purpose of the study?
This study is being done to explore the feasibility of conducting a study to examine the self-rated benefit of Gaviscon Advance taken four times daily, for the treatment of laryngopharyngeal reflux (LPR). LPR (sometimes referred to as “silent reflux”) can be a cause of vocal symptoms in some people. Gaviscon Advance is usually recommended to be taken for two months to manage these symptoms, but some people who take it find that their symptoms improve in a shorter time frame. This study examines changes to people’s symptoms every week to see whether Gaviscon Advance can be taken for less than two months, but with the same benefits. All patients being referred to Speech and Language Therapy from an Ear, Nose and Throat (ENT) Consultant for management of vocal symptoms will be invited to take part.

Who is organising the research?
This project is being carried out as part of a Voice Masters through the Clinical Speech & Language Therapy Department in Trinity College Dublin.

What will happen during the study?
- You have already consented to partake in the first stage of the study. This involved completing the Reflux Symptom Score questionnaire and reviewing the other eligibility criteria with the Principal Investigator.
- Now that you have been deemed eligible to participate, you will be randomly assigned to the ‘Treatment’ group or the ‘Control’ group.
Participants in the ‘Treatment’ group will buy a bottle of liquid Gaviscon Advance. Participants in this group are responsible for the cost of purchasing Gaviscon Advance. A 500ml bottle costs between €11.95-13.50. They will take 10mls of Gaviscon Advance four times daily (once after breakfast, lunch and dinner and a final fourth dose before bed) until their initial Speech and Language Therapy appointment. This Gaviscon Advance protocol has been clinically proven as a treatment in the management of laryngopharyngeal reflux.

The ‘Control’ group will have no treatment while awaiting their initial SLT assessment

Both the ‘Treatment’ group and the ‘Control’ group will repeat the Reflux Symptom Score questionnaire every week until their initial SLT appointment.

The Reflux Symptom Score self-rating questionnaire can be done online or submitted via email or post, with weekly reminders

The questionnaire should take a total of 2-5 minutes to complete each week

**How many people will take part in the study?**
We are aiming to recruit over 84 participants for this study.

**What do I have to do?**
By this stage, you will have consented to and completed the Reflux Symptom Score. The principal investigator Kate Grehan has contacted you to review the results of the Reflux Symptom Score and the additional exclusion criteria and you have been deemed eligible to participate in the next stage of the study.

You will now be given 2-3 days to review this Participant Information Leaflet. You will then be contacted by Kate Grehan again. If you consent to participate, you will be asked to sign the attached consent form and post or email it to Kate at Physiotherapy Department, Suite 20, Beacon Hospital or Kate.Grehan@beaconhospital.ie. Following that, you will be randomly assigned to either the ‘Treatment’ group or ‘Control’ group. Both groups will repeat the Reflux Symptom Score weekly, while awaiting their initial Speech and Language Therapy appointment. The questionnaires can be emailed or posted to Kate.Grehan@beaconhospital.ie or done online at whatever location is convenient for you with internet access. The ‘Treatment’ group participants will buy a bottle of Gaviscon Advance and take this four times daily (once after each meal and once before bed) until their initial SLT appointment.

**How long will I be on the study?**
The study will take between 1-8 weeks and is determined by how long you are waiting for your initial Speech and Language Therapy (SLT) assessment. It will cease once you attend for your initial SLT assessment. The current waiting list for an initial SLT assessment is 1-8 weeks, so it will not add any additional waiting time to participate in the study.

**Do I have to take part?**
No, it is up to you to decide whether or not to take part. If you do decide to take part you will be asked to sign the attached consent form and be given a copy of this information leaflet to keep. If you decide to take part but later change your mind, you are free to withdraw at any time without giving a reason. This will not affect the standard of care you receive. Likewise, the Primary Investigator may decide to withdraw you from the trial if it is in your best interest.

**What are the alternatives for treatment?**
If you decide not to participate, you will just wait for your initial Speech and Language Therapy assessment as is standard practice.

**What are the possible risks/side effects of participating in this study?**
Gaviscon Advance is an over-the-counter medication. Side effects of Gaviscon Advance are reported to be very rare. Patients are advised not to take Gaviscon Advance if they have a known allergy to any of the ingredients listed on the packaging. According to the manufacturer, the very rare side effects include allergic reactions such as
- Anaphylactic and anaphylactoid reactions (severe allergic reaction).
- Hypersensitivity reactions such as urticaria (hives).
- Respiratory effects such as bronchospasm (difficulty breathing).

Gaviscon Advance is considered high in sodium. Therefore, people on a low sodium diet will be excluded from this study. If you are on a low potassium or low calcium diet you must discuss taking Gaviscon Advance with your doctor before participating in the study.

You must leave a time-interval of 2 hours between taking Gaviscon Advance and other medicines, especially tetracyclines, fluoroquinolones, iron salts, thyroid hormones, chloroquine, bisphosphonates, and estramustine. If you are on any current medications, you should check whether any of them belong to these categories by asking your pharmacist or doctor.

There are no potential risks to participants who are in the Control group as a result of this study.

**What are the possible benefits from taking part in this study?**
Gaviscon Advance is a proven treatment option in the management of laryngopharyngeal reflux (LPR). This is usually recommended following initial SLT assessment. By participating in this study, participants in the Treatment group will receive treatment for their symptoms sooner than they usually would. Research using this data will help us better understand the assessment, treatment and management of reflux-related vocal symptoms. Participants in the Control group are not at a disadvantage, as people awaiting an initial Speech and Language Therapy (SLT) assessment do not typically have any intervention until they have attended their full SLT appointment.

**Can I stop being in the study?**
Yes, you can decide to stop at any time. This will not affect the standard of care you receive.

**Can anyone else stop me from being in the study?**
The study primary investigator or your doctor may stop you from taking part in this study at any time if:
- It is in the best interest for your health
- You do not follow your responsibilities for taking part in the study
- It is discovered at a later time that you do not meet the study participation requirements
- You need treatment not allowed in the study
- Administrative reasons require your withdrawal

**What happens if I am injured because I took part in this study?**
Adverse side effects of Gaviscon Advance are reported to be very rare.
In the unlikely event of adverse effects:
1. Stop taking Gaviscon Advance immediately. There are no negative side effects to suddenly discontinuing Gaviscon Advance.
2. Contact your doctor to inform them and seek their advice
3. Contact the Primary Investigator Kate Grehan on 01 293 8699 or Kate.Grehan@beaconhospital.ie.

**Will my taking part in this study be kept confidential?**

Your privacy is important to us. We take many steps to make sure that we protect your confidentiality and keep your data safe. The personal data that we collect about you for the purpose of the research study will be kept strictly confidential. You will be provided with a participant Identification (ID) number. This ID number will be used to store your personal data. The personal data that we will collect is your name, gender, age, Beacon Hospital medical number, telephone number, email address, ENT diagnosis, consent form and weekly Reflux Symptom Score (RSS) questionnaire results. This data will be saved on password protected and encrypted excel document or folder. The excel document and folder will be saved in Beacon UCD Academy drive. The Principal Investigator have access to this data. The two research assistants (Senior Speech and Language Therapists Aimée Holden and Kerrie Mc Carthy) may access this data if it is relevant to your Speech and Language Therapy management or should the Principal Investigator be unavailable. Data will also be coded to ensure anonymity and uploaded to a password protected and encrypted Trinity College One Drive cloud folder. Only the two investigators (Kate Grehan and Dr. Ciarán Kenny) will have access to this. No identifiable information will be saved on to local computer or laptops. No paper copies of any data will be kept.

The Principal Investigator, Research Supervisor and Research Assistants involved in this project have been trained in data protection law and are bound by Speech and Language Therapy professional codes of conduct.

A data protection impact assessment has been carried out indicating a low risk level.

If something did go wrong, we would contact the Data Controller and participants involved immediately.

Your personal details and ENT referral will also be stored on the Beacon Hospital electronic patient records system. This is standard practice of care for any patients of Beacon Hospital and is unrelated to the research study.

Data will be stored securely and confidentially with a participant ID number for the duration of the research study until the conclusion of the study (June 2023). This data will be retained for a further 5 years. After this time, any retained data will either be completely anonymised, meaning the code sheet with the Participant Identification Numbers will be destroyed. Anonymised data may be published in future scientific or medical journals. If you do not consent to your data being anonymized and retained for future use, your data will be destroyed securely after a period of 5 years.

A summary of study procedures will be stored on your medical notes as part of your SLT management.

According to data protection legislation we are required to inform you of the legal basis for using your personal data. The tasks we are performing are considered to be in the public interest. Some data is defined as more sensitive (such as ENT diagnosis, consent forms and Reflux Symptom Index/Reflux Symptom Score questionnaires) and are solely being collected for scientific research purposes and will be protected as per the above information.
You are entitled to:

- The right to access your data and receive a copy of it
- The right to have your data transferred to another organisation or “data controller”
- The right to restrict or object to processing of your data
- The right to object to any further processing of the information we hold about you (except where it is de-identified)
- The right to have inaccurate information about you corrected or deleted
- The right to request deletion of your data

By law you can exercise these rights in relation to your personal data, unless the request would make it impossible or very difficult to conduct the research. You can exercise these rights by contacting Trinity College Data Protection Officer, Secretary’s Office, Trinity College Dublin, dataprotection@tcd.ie.

**What are the costs of taking part in this study?**
There are minimal costs associated with this study. If you chose to print and post the forms, you will have to cover the cost of this. Participants in the Treatment Group will have to cover the cost of Gaviscon Advance. You will not be paid for your participation in this study.

**What about future use of my sample for research?**
Due to the nature of this research it is likely that other researchers may find the data collected to be useful in answering future research questions about the assessment and management of laryngopharyngeal reflux. Any data used for future research purposes will be irrevocably anonymized. We will ask for your explicit consent for your data to be used in this way. You do not have to agree to have your data available for future research. Future research will only take place if it has research ethics approval.

**Who has reviewed and approved this study?**
This study has been reviewed and approved by Beacon Hospital Research Ethics Committee and Trinity College Research Ethics Committee.

If you have any concerns or questions you can contact:

5. Principal Investigator: Kate Grehan, Senior Speech and Language Therapist, Beacon Hospital on 01 2938699 or Error! Hyperlink reference not valid.
6. Research Supervisor: Dr Ciarán Kenny, Clinical Speech and Language Studies, Trinity College Dublin on Error! Hyperlink reference not valid.
7. Data Protection Officer, Trinity College Dublin: Data Protection Officer, Secretary’s Office, Trinity College Dublin, Dublin 2. Email: Error! Hyperlink reference not valid. Website: Error! Hyperlink reference not valid.
8. Mr Brian Fitzgerald, Data Protection Officer, Beacon Hospital, Sandyford, Dublin 18
   Under GDPR, if you are not satisfied with how your data is being processed you have the right to lodge a complaint with the Office of the Data Protection Commission, 21 Fitzwilliam Square South, Dublin 2.
Appendix E 2nd Consent form

Informed Consent Form
A pilot randomised trial on the effect of Gaviscon Advance on laryngopharyngeal reflux symptoms in adults referred to an outpatient Speech and Language Therapy service

Primary Investigator Name: Kate Grehan
Hospital Name: Beacon Hospital

Participant Identification Number: ____________________

1. I confirm that I have been given a copy of all 5 pages of the Patient Information Leaflet and Consent form. I have read the patient information leaflet and consent form or it has been read to me. This information was explained to me and my questions were answered.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my medical care or legal rights being affected.

3. I understand that relevant parts of my medical records may be seen by Kate Grehan, Senior Speech and Language Therapist and two research assistants from the Speech and Language Therapy Department Aimée Holden and Kerrie Mc Carthy, where it is relevant to the research. I agree that these individuals can access my records.

4. I understand and give informed consent that data related to me collected during this study will be processed and analysed as is required by this clinical study and according to the Data Protection Act.

5. I understand that my data may be used for research as described in the Patient Information Leaflet.

6. I agree to my GP and ENT consultant being informed of my involvement in this study

7. I voluntarily agree to take part in this study having been fully informed of the risks, benefits and alternatives.

Please initial the appropriate box:

- I agree that my data may be coded and retained for a minimum of 5 years post-study as per Beacon Hospital policy.
- I DO NOT AGREE that my data may be coded and kept for future use and would like my data to be destroyed after the study concludes
- I understand I will not be entitled to a share of any profits that may arise from the future use of my material/data or products derived from it.
- I give permission for material/data to be anonymised after the 5 year period and stored for possible future research unrelated to the current study without further consent being required but only if the research is approved by a Research Ethics Committee.

____________________  ____________________  ____________________
Name of Patient (Print)  Signature of Patient  Date

____________________  ____________________  ____________________
Name of Investigator (Print)  Signature of Investigator  Date
Appendix F Reflux Symptom Score

This section asks about symptoms you may be having related to your ear, nose or throat. When answering the questions below, please circle a number from 0 to 5. You can interpret these numbers using this scale as follows.

**Frequency:**
- 0 - I have not had this problem in the last month.
- 1 - I have had this problem 1-2 times per week in the last month.
- 2 - I have had this problem 2-3 times per week in the last month.
- 3 - I have had this problem 3-4 times per week in the last month.
- 4 - I have had this problem 4-5 times per week in the last month.
- 5 - I have had this problem daily in the last month.

**Severity:**
This is a scale from 0 (problem is not severe) to 5 (problem is very troublesome when it occurs). Choose the number that fits for you.

**Quality of Life Impact:**
This is a scale from 0 (least impact on your life) to 5 (most impact on your life).

<table>
<thead>
<tr>
<th>Ear, Nose &amp; Throat Symptoms</th>
<th>Frequency</th>
<th>Severity</th>
<th>Total</th>
<th>QOL Impact</th>
<th>QOL Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hoarseness/ voice problem</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>2. Throat pain</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>3. Pain when swallowing</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
</tbody>
</table>
4. Difficulty swallowing | 0 1 2 3 4 5 | 0 1 2 3 4 5 | 0 1 2 3 4 5  
5. Throat clearing | 0 1 2 3 4 5 | 0 1 2 3 4 5 | 0 1 2 3 4 5  
6. Sensation of something sticking in your throat | 0 1 2 3 4 5 | 0 1 2 3 4 5 | 0 1 2 3 4 5  
7. Excess mucous in the throat or postnasal drip sensation | 0 1 2 3 4 5 | 0 1 2 3 4 5 | 0 1 2 3 4 5  
8. Ear pressure/pain (day or night) | 0 1 2 3 4 5 | 0 1 2 3 4 5 | 0 1 2 3 4 5  
9. Tongue burning | 0 1 2 3 4 5 | 0 1 2 3 4 5 | 0 1 2 3 4 5  
10. Other | 0 1 2 3 4 5 | 0 1 2 3 4 5 | 0 1 2 3 4 5  

This section asks about symptoms you may be having related to your abdomen. When answering the questions below, please circle a number from 0 to 5 (see above scale).

<table>
<thead>
<tr>
<th>Abdominal symptoms</th>
<th>Frequency</th>
<th>Severity</th>
<th>Total</th>
<th>QOL impact</th>
<th>QOL Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Heartburn, stomach acid</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Regurgitation of liquids, solids or burps</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Abdominal pain</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Diarrhoea</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Constipation</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Indigestion</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
This section asks about symptoms you may be having related to your chest and breathing. When answering the questions below, please circle a number from 0 to 5 (see above scale).

<table>
<thead>
<tr>
<th>Respiratory Symptoms</th>
<th>Frequency</th>
<th>Severity</th>
<th>Total</th>
<th>QOL impact</th>
<th>QOL Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cough after eating or lying down</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Cough (daytime)</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Breathing difficulties, breathlessness or wheezing</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Chest pain</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Other</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RSS Total Score: ..................  QOL Score: ..................
**Appendix G Participant Instructions**

| Treatment group | You have been randomly assigned to the treatment group. This means you need to buy a bottle of Gaviscon Advance from your pharmacy today. You must start the Gaviscon Advance protocol tomorrow. The protocol is as follows:  
  - 10mls Gaviscon Advance after breakfast  
  - 10mls Gaviscon Advance after lunch  
  - 10mls Gaviscon Advance after dinner  
  - 10mls Gaviscon Advance before bed  
  You will continue this protocol until you attend for your initial Speech and Language Therapy Appointment  
  You must complete the Reflux Symptom Score questionnaire weekly. You will receive an email or phone call to remind you each week.  
  *Please refer to the Gaviscon Advance information leaflet for further information on considerations when taking Gaviscon Advance.  
  ** If you have any queries please do not hesitate to contact the Principal Investigator Kate Grehan on [Kate.Grehan@beaconhospital.ie](mailto:Kate.Grehan@beaconhospital.ie)  
  ***If you notice any adverse effects from taking Gaviscon Advance please stop taking it, contact your doctor if necessary and the Principal Investigator |
|-----------------|-------------------------------------------------------------------------------------------------|
| Control group   | You have been randomly assigned to the control group. This means that you do not have to take any treatment or make any special changes while awaiting your initial Speech and Language Therapy appointment.  
  You must complete the Reflux Symptom Score questionnaire weekly. You will receive an email or phone call to remind you each week.  
  *If you have any queries please do not hesitate to contact the Principal Investigator Kate Grehan on [Kate.Grehan@beaconhospital.ie](mailto:Kate.Grehan@beaconhospital.ie) |
Appendix H Ethical Approval TCD

Trinity College Dublin
Coláiste na Trionóide, Baile Átha Cliath
The University of Dublin

Application  Academic Year 2019/20
Applicant Code  TT37
Applicant/Supervisor Name  Kate Grehan / Dr Ciarán Kenny
Title of Research  Effects of Gaviscon Advance on laryngopharyngeal reflux symptoms
Date of this letter  02/07/2020

Dear Kate,

Your amended submission (dated 30/06/2020) for ethical approval for the research project above was considered by the Research Ethics Committee, School of Linguistic, Speech and Communication Sciences, Trinity College Dublin and has been approved in full.

Please note:
(i) On completion of research projects, applicants should complete the End of Project Report Form (which can be found at: https://www.tcd.ie/slisce/research/ethics/) and submit one signed hard copy to the School Office (Room 4091, Arts Building) as well as an electronic copy (to slisce@tcd.ie)
(ii) The REC requests, in particular, that you attend to your commitments regarding the storage and destruction of data arising from this research, in keeping with REC policy and General Data Protection Regulation (GDPR) guidelines.

We wish you every luck with your research.

Best wishes,

Dr Ciarán Kenny
Chair, Research Ethics Committee
School of Linguistic, Speech and Communication Sciences
Appendix I Ethical Approval Beacon Hospital

Ms Kate Grehan
Dept of Physiotherapy
Beacon Hospital
Sandyford
Dublin

Date: 21st September 2020

BHREC Ref: BEAD149

Study Title: Effects of Gaviscon Advance on laryngopharyngeal reflux symptoms: A randomised controlled study.

Dear Ms Grehan,

The Beacon Hospital Research Ethics Committee (BHREC) received your application on 23rd July 2020 and reviewed it at their meeting on the 13th August 2020.

Following review of your recently submitted amendments, the Vice Chair of the BHREC, Assoc Prof David Burke has given your study Full Approval to proceed.

The submission has been reviewed from an ethical perspective only. It is the responsibility of the PI/sponsor/data controller to ensure and monitor compliance with any relevant data protection legislation in the country where the study is due to take place and or with any local policy in the site where the study is being conducted.

The application was reviewed by the Beacon Hospital Data Protection Committee and the Data Protection Officer, Mr Brian Fitzgerald.

The documents submitted, reviewed and approved are listed as follows:

Initial Submission:
Beacon-Hospital-Ethics Application 24.07.20

Amendments:
- 2019-2020 TW/MCPL (Research Activities)
- Beacon-Hospital-Ethics-Application 06.05.20 Clean
- Beacon-Hospital-Ethics-Application 06.05.20 Tracked
- Beacon-Hospital-Ethics-Application 17.05.20 CLEAN
- Beacon-Hospital-Ethics-Application 17.05.20 TRACKED
- FW_Next research meeting
- PIIL and Consent form 1 17.09.20 Clean
- PIIL and Consent form 2 17.09.20 Clean
- PIIL and Consent form 1 17.09.20 Tracked
- PIIL and Consent form 2 17.09.20 Tracked
- TT27 – REC Full approval Following Amendments [5543]
Approval will be rescinded if the following terms are also not adhered to:

- **Annual Progress Reports** must be submitted to the REC for the duration of the project, with the first report due within a period of no later than 12 months from the date of this letter.

- **A Final Report** must be submitted to the REC following completion of the project.

- All application/protocol amendments must be submitted for review and approval to the REC prior to implementation.

- The REC must be notified of all any **Serious Adverse Events (SAEs)** or new issues/events likely to affect the conduct or safety of the study and/or participants.

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assoc Prof David Burke</td>
<td>Vice Chair, REC, Beacon Hospital</td>
<td></td>
<td>24/3/2023</td>
</tr>
<tr>
<td>Mr. Brian Fitzgerald</td>
<td>Data Protection Officer</td>
<td></td>
<td>12/10/20</td>
</tr>
</tbody>
</table>

Please acknowledge receipt of this letter and if you have any queries relating to the terms and conditions outlined in this letter, please do not hesitate to contact me.

Kind regards,

Beacon Hospital Research Ethics Committee Administrator
Beacon Hospital
Suite 13
Sandyford
Dublin 18

Email: ethics@beaconhospital.ie
Appendix J Letter to ENT/ GP

Referring ENT/ GP

Date

Re: Patient’s details

Dear Dr/Ms/Mr,

Many thanks for your referral for the above-named patient to Speech and Language Therapy. ___ is currently awaiting his/her initial SLT appointment. We are conducting a pilot trial on the use of Gaviscon Advance in managing vocal symptoms resulting from laryngopharyngeal or “silent” reflux. Gaviscon Advance taken in 10ml doses four times per day (after breakfast, lunch, dinner and before bed) has been proven to be effective in managing silent reflux over a two month period. In practice, we notice improvement in people’s symptoms sooner than the two month timeframe, but no studies have been conducted to look at this. In this research study, we are recruiting participants over a 1-8 week period while they are awaiting their initial SLT appointment. If patients are deemed to have silent reflux based on a score >13 in the self-rated Reflux Symptom Score and satisfy other criteria they will be invited to participate. The exclusion criteria are as follows:

- Current smoker
- Clinically significant neurological illness (this includes people with a cognitive impairment, diagnosis of Dementia or any person that may find it challenging to complete the weekly questionnaires as a result of a neurological illness)
- Significant gastrointestinal illness
- Upper respiratory tract infection in the past 1 month
- Currently using anti-reflux medication (e.g. proton pump inhibitor, alginate)
- Significant dysphagia
- On a salt restricted diet
- Undergoing any other medical investigations/ treatment for their symptoms.

___ has been found to meet the above criteria and has consented to participate in the study. He/she will be randomly assigned to either the treatment or control group. The treatment group will be advised to purchase and take 10mls Gaviscon Advance four times daily until their initial assessment, the control group will have no intervention (as is standard practice while awaiting an initial assessment appointment). Both groups will be asked to complete the Relux Symptom Score at weekly intervals. His/her participation in the study will cease once he/she attends for his/her initial assessment.

Participants have been advised on the potential risks associated with taking Gaviscon Advance in their Participant Information Leaflet (see attached). If for any reason they should not be taking this medication for or you have any other queries, please do not hesitate to contact me on 01 2938699 or Kate.Grehan@beaconhospital.ie.

Kind regards,

________________
Kate Grehan
Senior Speech and Language Therapist
Beacon Hospital