A RETROSPECTIVE ANALYSIS OF SUBJECTS WHO HAVE APPROVED GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD) FROM A PRIVATE MEDICAL AID FUND

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DEDICATION

TO MY FAMILY

DECLARATION

This document describes original work by the author and has not been submitted in any form to any other University. Where the work of other authors has been used, it has been duly acknowledged in the text.

The study was supervised by Prof. V. Rambiritch (PhD) Discipline of Pharmacology, University of Kwa Zulu Natal (Westville).

The information for the retrospective analysis of subjects diagnosed with Gastroesophageal reflux disease (GORD) was taken from a private medical aid, National Medical Plan (NMP) for the period January 2002 to December 2003.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

%	percent
<	less than
>	greater than
BSG	British Society of Gastroenterology
CI	confidence interval
COXIB	specific cyclo-oxygenase –2 inhibitors
COX 2	selective cyclo-oxygenase –2 inhibitors
DMARDS	Disease Modifying Anti-Rheumatic Drugs
ECG	electrocardiogramn
GIT	gastro-intestinal tract
GORD	gastro-oesophageal reflux disease
gr	gastroscopy
IT	Information Technology
MRC	Medical Research Council
n.s.	not significant
NCCP	noncardiac chest pain
NERD	non-erosive oesophageal reflux disease
NICE	National Institute of Clinical Excellence
NMP	National Medical Plan
NSAIDS	nonsteroidal anti-inflammatory drugs
OR	odds ratio
PPIs	proton pump inhibitors
PUD	Peptic ulcer disease
SAGES	South African Gastroenterologists Society
LOS	Lower oesophageal sphincter
H_2RA	H_2-receptor antagonists
Ach	acetylcholine
Camp	cyclic adenosine monophosphate
Ca^{2+}	calcium
ATPase	adenosine triphosphate
H	hydrogen
K	potassium
AGA	American Gastroenterological Association
OTC	over the counter
D	once daily

ABSTRACT

This study is a retrospective analysis of subjects diagnosed with gastro-oesophageal reflux disease (GORD) at a private medical aid namely, National Medical Plan (NMP), for the period January 2002 to December 2003. This study was an analysis of GORD and its complications, the use of gastroscopy as a staging criteria, cost of drug treatment, and concurrent diagnosis and concurrent drugs.

Subjects with alarming symptoms, complications of GORD and in whom symptoms have not resolved, need to have a gastroscopy performed. If left untreated, some of these could lead to more severe and serious complications. Accurate recognition of these symptoms will help to identify, evaluate and treat subjects timeously. The use of the gastroscopy allows for the detection of complications of GORD. This helps identify subjects with complications timeously and avoids, delays or stops the progression of the complications of GORD. The unnecessary use of gastroscopy in subjects without complications have caused costs to spiral out of control. Subjects without alarming symptoms or complications should be treated empirically with proton pump inhibitors (PPIs) to resolve the symptoms of GORD.

1753 subjects with GORD were identified. Those subjects that satisfied the inclusion criteria were divided into 2 subsets, those without gastroscopy (n=211) and those with gastroscopy (n=375). The latter group was further identified as those that had one (n=232) or more than one gastroscopy done (n=143). The choice of the study population was not based on the complication or the severity of the symptoms but on whether or not the attending doctor chose to have a gastroscopy done. All newly diagnosed GORD subjects were on continuous drug therapy for the 2 years. Non-compliant subjects who were treated for GORD previously and intermittently were excluded from the study.

The number of complications detected in subjects with more than 1 gastroscopy was the highest (34%; n=48) as compared to subjects with 1 gastroscopy (21%; n=49) or without gastroscopy (7%; n=15). The performance of gastroscopy in these subjects without gastroscopy (7%; n=15) may have resulted in more complications being detected. Having more than 1 gastroscopy increased the odds of detecting complications significantly compared to subjects with just one gastroscopy.

Gastroscopy contributed to the detection of 15.7% Barretts oesophagitis, 1.9% erosive oesophagitis, 3% oesophageal ulcers, and 3.4% oesophageal strictures. In subjects without gastroscopy, 2% Barretts oesophagitis, 0.5% erosive oesophagitis, 0.5% oesophageal ulcers, and 3% oesophageal strictures were detected. Barrett's oesophagus is a serious form of GORD, which may eventually lead to cancerous changes in the tissue lining of the oesophagus. This is a very serious consequence of GORD and needs to be treated appropriately. Subjects with complications of GORD need to use an objective criteria (gastroscopy) to detect complications and treat appropriately and timeously. The current practice of most physicians is to perform an endoscopic surveillance every 2 to 3 years in subjects with Barrett's oesophagus, with increased frequency if dysplasia is detected (Falk, 2000).

Those subjects with gastrosco y performed and with complications of GORD were more expensive to treat. However in the long term it is actually more cost effective due to the fact that complications will be treated timeously and the progression of the complications of GORD will be avoided. Some of the directly related concurrent medical conditions identified were diaphragmatic hernia, anaemia, and peptic ulcer. Osteoarthritis, osteoporosis and asthma were identified as indirectly related concurrent medical conditions. NSAIDS, calcium channel blockers, iron supplements, aspirin and alendronate were identified as drugs likely to adversely affect GORD.

This study was confined to a single medical aid society. For comparison, other medical aids should be included. Subjects without alarming symptoms (chronic gastrointestinal bleeding; progressive unintentional weight loss; progressive difficulty swallowing; persistent vomiting; iron deficiency a emia; epigastric mass or suspicious barium meal) should be treated empirically for 1-2 months, however if symptoms do not resolve or if subjects have complications, then only should a gastroscopy be performed (National Institute of Clinical Excellence GC017). Subjects with alarming symptoms, complications of GORD, or in whom symptoms have not resolved, require objective criteria (gastroscopy) to diagnose GORD. Gastroscopy should not be unnecessarily performed in subjects without the complications; instead the patient without alarming symptoms or complications should first be treated empirically.

CHAPTER ONE: INTRODUCTION

1.1 Background to problem

Gastro oesophageal reflux disease (GORD) occurs when the acid from the stomach refluxes into the oesophagus thus causing inflammation or injury to the oesophagus (Kahrilas, 2003). GORD is diagnosed by subjective (symptoms) and objective (gastroscopy, ambulatory pH monitoring) criteria. The oesophageal symptoms are characterised by heartburn, dysphagia, severe pain on swallowing (odynophagia), bloating, nausea, epigastric pain, early satiety and the extra-oesophageal symptoms are characterised by wheezing, cough, hoarseness, sore throat, choking and chest pain.

When a patient experiences the symptoms of GORD, the first option would appear to be for a gastroscopy to be performed. Subjects without alarming symptoms should be treated empirically for 2 months. Most subjects experience relief from symptoms of GORD after a few months of PPI treatment. However, subjects with complications of GORD (erosive oesophagitis, ulcerative oesophagitis, oesophageal strictures, Barrett's oesophagus and oesophageal adenocarcinoma) or in whom symptoms have not resolved, require a gastroscopy to be performed. A second gastroscopy may need to be undertaken to evaluate for underlying Barrett's oesophagus that may have been missed on the initial examination (Fennerty, 2003). Subjects with erosive oesophagitis are at risk of complications of oesophagitis, including bleeding, stricture and Barrett's oesophagus (Schneider, 2002) thus requiring follow up gastroscopy evaluations. This applies to oesophageal ulcers and strictures as well.

It is vital to perform an early endoscopic screening and surveillance in subjects with Barrett's oesophagus and oesophageal adenocarcinoma. The aim of endoscopic screening and surveillance is to dysplasia. The goal of such monitoring is to improve early recognition of invasive oesophageal cancer, at a curable stage (Falk, 1999). It seems more expensive to treat subjects with complications of GORD. But in the long term it is actually more cost effective, due to the fact that complications will be treated timeously and the progression of the complications of GORD will be avoided.

PPIs have been documented to be superior to H_2-receptor antagonists (H_2RA) in meta-analyses for the healing of erosive oesophagitis (Sharma, 2003). The Genval Workshop

Guideline and National Institute of Clinical Excellence (NICE GC017) guidelines also recommend PPI therapy as the initial medical treatment of choice for GORD. It is cost effective and clinically appropriate to empirically treat subjects without alarming symptoms and complications of GORD.

1.2 Motivation

GORD can severely affect a subject's quality of life and therefore needs to be treated appropriately. Uncomplicated GORD seems to affect the majority of subjects. These subjects could be successfully treated empirically for two months. However, subjects with complications of GORD and in whom symptoms have not resolved, need to have a gastroscopy performed. If left untreated, some of these could lead to more severe complications for example Barretts oesophagus and adenocarcinomas. Accurate recognition of these symptoms will help to identify, evaluate and treat subjects timeously. The use of the gastroscopy allows for the detection of complications of GORD. This helps identify subjects with complications timeously and avoids, delays or stops the progression of the complications of GORD. The study retrospectively analyses subjects with and without complications where a gastroscopy may or may not have been done.

Ulcerative oesophagitis, oesophageal erosions, oesophageal stricture and Barretts oesophagus are serious complications of GORD. Ulcerative oesophagitis requires aggressive treatment to ensure quicker healing time. These subjects are more likely to develop complications and become more resistant to treatment (Reynolds, 1996). Subjects with oesophageal stricture and oesophageal erosions may need a follow up gastroscopy to evaluate for the presence of Barretts oesophagus, which could have been missed on initial examination. This may occur because erosions and ulcers may obscure underlying Barretts oesophagus. Thus it is important to treat oesophageal stricture and oesophageal erosions timeously since this condition leads to more serious complications.

Barretts oesophagus is a serious complication that could lead to an even more serious complication namely oesophageal adenocarcinoma. Treatment of GORD in subjects with Barrett's oesophagus has not been shown to eliminate metaplasia of the oesophagus. Therefore subjects with Barrett's oesophagus require periodic endoscopic biopsy to assess oesophageal tissue for malignant changes. These subjects often remain asymptomatic until the development of an associated complication (strictures, adenocarcinoma) (Nevin, 2000).

This further emphasises the need for gastroscopies in subjects with complications. It is recommended for subjects without dysplasia to have a gastroscopy performed every 2-3 years (Sampliner, 1998). However subjects with low-grade dysplasia require annual surveillance and those with high-grade dysplasia, surveillance every 3 months is appropriate (Gopal, 2001; Valdivia and Fogel 2003).

Subjects without alarming symptoms should be treated for 2 months, since most of the symptoms may have resolved after empirical therapy. This avoids the cost of the gastroscopy and other associated medical costs. Subjects with complications require treatment for a longer period of time due to the mucosal damage that has occurred over a period of time, which has lead to serious complications (Barrets oesophagus, oesophageal strictures).

It seems less expensive to treat those subjects without gastroscopy. However, based on pharmacoeconomic principles, it costs more in the long term to treat subjects who did not have a gastroscopy performed. Undetected and therefore untreated complications result in resistance to treatment, prolonging healing time, which may lead to Barrets oesophagus and adenocarcinoma. This results in costs escalating. There is a need for gastroscopy in subjects with complications and in whom symptoms have not resolved. Although the subset with gastroscopy is more costly, in the long term it is more cost effective since the complications will be detected and treated timeously and effectively.

It is recommended by the NICE guidelines that routine endoscopic investigation of subjects of any age, presenting with dyspepsia and without alarming signs, is not necessary. These subjects should be treated empirically for approximately 1-2 months before having a gastroscopy. If the symptoms persist, or if there are complications of GORD then only should a gastroscopy be performed (CG017NICE guideline). These guidelines were followed in some subjects but needs to be enforced for pharmacoeconomic reasons.

1.3 Aim

A retrospective analysis of the treatment of subjects with gastro-oesophageal reflux disease (GORD) approved from a private medical aid fund.

1.4 Objective

- To establish whether the staging criteria (gastroscopy) has been met in the diagnosis of GORD
- To evaluate treatment
- To determine a cost analysis
- To evaluate the complications of GORD

CHAPTER TWO: LITERATURE SURVEY

GORD occurs when the acid from the stomach move backward into the oesophagus. This action is called reflux. Reflux occurs if the muscular actions in the oesophagus or other protective mechanisms fail, thus causing inflammation or injury to the oesophagus (Simon, 2002; Kahrilas, 2003).

The lining of the oesophagus offers a weak defence when acid and enzymes reflux into the oesophag s. The oesophagus is protected using specific muscles. The lower oesophageal sphincter (LOS) is a band of muscle around the bottom of the oesophagus where it meets the stomach. The LOS opens to let food enter the stomach and then immediately closes to prevent regurgitation of the stomach contents. The LOS also maintains this pressure barrier until food is swallowed again. The peristaltic action of the oesophagus serves as an additional defence mechanism and pushes the contents back down into the stomach (Simon, 2002).

Oesophagitis refers to when acid reflux causes irritation or inflammation in the oesophagus. Erosive oesophagus occurs if the damage becomes extensive and injures the oesophagus. Symptoms of GORD can occur without any signs of inflammation or injury to the oesophagus. This condition is referred to as non-erosive oesophageal reflux disease (NERD). NERD rarely progresses to GORD. In NERD, subjects have no signs of inflammation or erosion in the oesophagus, but they experience certain symptoms of GORD, such as burning sensations behind the breastbone for at least three months (Simon, 2002). They are unlikely to develop complications of reflux such as stricture, bleeding and Barrett's oesophagus (Schneider, 2003).

2.1 Epidemiology

GORD is generally considered to be one of the most prevalent conditions affecting the gastrointestinal tract; however, figures on the precise prevalence and incidence of GORD are based more on estimates than actual data. According to the National Digestive Diseases Information Clearinghouse (USA) (2005), the prevalence of GORD and related oesophageal disorders where reflux symptoms occurred at least weekly was 20 percent of the U.S. population.

According to Voutilainen (2002), there are nearly an equal proportion of men and women affected. However, in Barret's oesophagus, there is a predominance of white males (Gopal, 2001). Increa ing age is an important factor in the prevalence of GORD which may be the result of the cumulative acid injury to the oesophagus over time (Collin et al., 1995).

International studies show that GORD occurs more frequently in the white population rather than the African population. Complicated GORD appears to be predominantly a disorder of whites (Spechler, 2002). A study conducted at Chris Hani Baragwanath Hospital concluded that urbanization had increased the risk associated with the development of GORD in blacks. However, one would have expected this to lead to an increase in this disease among Africans, but this increase has not happened (Segal, 2001).

The National Guideline Clearinghouse has summarised the two evidence-based publications on the diagnosis and management of gastro-oesophageal reflux (Good et al., 2003). One was developed by the American College of Gastroenterology and revised in June 1999, and the other prepared by an international panel of experts participating in the Genval Workshop (Good et al., 2003). In these publications, the prevelence of Barrett's oesophagus was between 10% to 15%, oesophageal strictures were 4% to 20%, oesophageal ulceration were 2%-7% and adenocarcinaoma with Barrett's esophagus was 0.5%.

2.2 Pathophysiology

GORD occurs when the normal antireflux barrier between the stomach and the oesophagus is impaired. Lower oesophageal sphincter (LOS) incompetence, transient lower oesophageal sphincter relaxation and hiatal hernia are the primary factors involved in the development of GORD. Acid, pepsin, bile acids, and trypsin in the gastro-duodenal contents adversely affect the oesophageal defence thus resulting in the symptoms of GORD. As more components of oesophageal defence break down, the severity of reflux increases (Vollweiler and Falk, 2003).

2.2.1 Transient LOS relaxation

Transient LOS relaxation is the mechanism by which reflux occurs in healthy people. Most subjects with GORD have a normal resting LOS tone. Transient LOS relaxation is the

dominant cause of reflux in these subjects. They occur via stimulation of vagal sensory and motor nerves in response to gastric distention (Kahrilas, 2003; Szarka, 1999).

2.2.2 Decreased resting tone of lower oesophageal sphincter

The lower oesophageal sphincter is the primary barrier to reflux. Subjects with GORD have a weak, low-pressure LOS, which allows reflux to occur every time the pressure in the stomach exceeds that in the LOS. This condition is present in a minority of GORD cases, and is usually associated with severe oesophagitis. Factors that decrease LOS tone include endogenous hormones, medications and specific foods (Kahrilas, 2003; Szarka, 1999).

2.2.3 Decreased salivation

Saliva is alkaline and can normally neutralize the acid coating the oesophagus after a secondary peristaltic wave. Therefore, decreased salivation can contribute to the duration of oesophageal acid exposure (Kahrilas, 2003).

2.2.4 Impaired oesophageal clearance

Oesophageal acid clearance is affected by peristalsis and saliva. Peristalsis clears gastric fluid from the oesophagus, and swallowing saliva neutralizes any remaining acid. Ineffective oesophageal acid clearance increases oesophageal acid exposure time in subjects with GORD. According to Kahrilas (1998), in an experimental study, subjects with GORD have been found to have acid clearance times that are two to three times longer than those of persons without GORD. Peristaltic dysfunction is due to failed peristalsis and low-amplitude contractions. This leads to incomplete oesophageal emptying. Peristaltic dysfunction often increases with increasing severity of oesophagitis. Salivation restores oesophageal pH and completes oesophageal acid clearance. Acid clearance is prolonged by a reduced salivary rate or by diminished salivary capacity to neutralize acid (Kahrilas, 2003; Scott, 1999). The oesophageal acid exposure determines the oesophageal mucosal injury (Kahrilas, 2003; Simon, 2002) and the frequency and severity of symptoms such as heartburn, regurgitation, and pain. The acidic pH of the refluxed gastric material causes oesophageal mucosal injury, which is linked to increasing GORD severity (Kahrilas, 2003; Scott, 1999).

2.2.5 Impaired tissue resistance

Reflux occurs depending on the ability of the oesophageal mucosa to withstand injury. This is influenced by the age and nutritional status of the individual. Oesophageal tissue protects against injury by limiting the rate of diffusion of hydrogen ions into the epithelium. The oesophagus produces bicarbonate and mucus. Bicarbonate buffers the acid, and mucus forms a protective barrier on the epithelial surface. Oesophageal mucosa is more prone to acid damage in comparison to the stomach lining. With the reflux of gastric content, the acid and pepsin cause mucosal damage, which exceeds the level of mucosal protection (Kahrilas, 2003).

2.2.6 Delayed gastric emptying

If gastric emptying is delayed, the gastric fluid volume is increased. Delayed gastric emptying is believed to contr bute to a small proportion of GORD cases by increasing the amount of fluid available for reflux (Kahrilas, 2003; Simon, 2002).

2.2.7 Other causes of GORD

- Hiatal Hernia
- Genetic Factors
- Inter-relation between asthma and GORD
- Drugs that increase the risk of GORD for example nonsteroidal anti-inflammatory drugs (NSAIDs), bisphosphonates and calcium channel blockers.
- Lifestyle factors can also result in an increased risk of reflux. Smoking, large meals, fatty foods, caffeine, pregnancy, obesity, body position, and hormones may all exacerbate GORD (Simon, 2002).

2.3 Symptoms

2.3.1 Oesophageal symptoms

2.3.1.1 Heartburn

Heartburn is the most common symptom of GORD (Kahrilas, 2003; Vaezi, 2005). It presents as a substernal burning sensation, and usually occurs after meals or when reclining at bedtime. Heartburn is caused by acid stimulation of sensory nerve endings in the deeper layers of the oesoph geal epithelium. Prolonged contact of excessive amounts of acid injures the oesophagus and produces a burning sensation. Heartburn is considered as one of the classic symptoms of GORD (Kahrilas, 2003; Kinnear, 1999).

2.3.1.2 Regurgitation

GORD commonly presents as regurgitation (Vaezi, 2005). Acid regurgitation is the return of acidic gastric contents into the oesophagus without nausea, wretching, or abdominal contractions. If reflux of injurious acidic gastric contents extends beyond the oesophagus to the lungs, larynx, pharynx, or oral cavity, extra-oesophageal GORD symptoms can occur. Regurgitation is considered as one of the classic symptoms of GORD (Kahrilas, 2003; Kinnear, 1999).

2.3.1.3 Dysfunctional swallowing

Dysphagia and odynophagia are symptoms of dysfunctional swallowing. Dysphagia is the perception of impaired movement of swallowed material from the pharynx to the stomach. It affects more than 30% of subjects with GORD. Dysphagia describes a feeling of food getting stuck. Dysphagia may occur due to abnormal peristalsis, inflammation or a stricture. Subjects with dysphagia should be diagnostically investigated for oesophageal cancer. Odynophagia is a sharp substernal pain that occurs during swallowing. The pain may be so severe as to limit oral intake. The cause of odynophagia is oesophageal ulceration (Kahrilas, 2003).

Other symptoms include bloating, nausea, epigastric pain, and early satiety.

2.3.2 Extra-oesophageal symptoms

2.3.2.1 Non cardiac Chest pain (NCCP)

Noncardiac chest pain refers to unexplained substernal chest pain resembling a myocardial infarction without evidence of coronary artery disease. The pain could be caused by the stimulation of chemoreceptors, or by the distention of the oesophagus. Chest pain caused by reflux may present with sharp or dull pain and may radiate widely into the neck, arms or back (Kahrilas, 2003; Vaezi, 2005).

2.3.2.2 Pulmonary symptoms

Symptoms include asthma, chronic coughing, bronchitis and wheezing. This occurs when refluxed material gets past the upper oesophageal sphincter and aspirates into the larynx and tracheobronchial tree (Kahrilas, 2003). GORD symptoms are significantly associated with asthma and patients with asthma have increased dysphagia, hoarseness, and antireflux medication use (Sharma, 2003).

2.3.2.3 Oral symptoms

Gingivitis, halitosis and tooth decay are caused by contact with acidic refluxate (Kahrilas, 2003).

2.3.2.4 Throat symptoms

Symptoms include hoarseness, laryngitis, and sore throat. Damage to the larynx is caused by acidic refluxate (Kahrilas, 2003; Sharma, 2003).

2.3.2.5 Ear symptoms

Symptoms include earache, which may result due to acid damage to the oropharynx.

2.4 Complications

2.4.1 Oesophageal complications

2.4.1.1 Erosive oesophagitis

When the acid causes irritation or inflammation, the condition is called oesophagitis. If the damage becomes extensive and injures the oesophagus, the disorder is known as erosive oesophagitis. Oesophageal erosions are breaks in the lining of the oesophagus, which are due to acidic reflux in the oesophagus. Oesophageal erosions are excavated defects in the oesophageal mucosa that result when epithelial cells succumb to the caustic effects of refluxed acid and pepsin (Spechler, 2003). Subjects with erosive oesophagitis are at risk of complications of oesophagitis, including bleeding, stricture and Barrett's oesophagus (Schneider, 2002).

It is important to treat erosive oesophagitis timeously since this complication leads to more serious complications. Subjects with erosive oesophagitis on an initial endoscopic examination will need follow-up to evaluate for underlying Barrett's oesophagus that may have been missed on the initial examination (i.e. because the presence of mucosal erosions/ulcerations may have obscured the identification of underlying Barrett's disease) (Fennerty, 2003).

Proton-pump inhibitors (PPIs) form the cornerstone of treatment for erosive oesophagitis and have been documented to be superior to H_2-receptor antagonists (H_2RAs) in meta-analyses for the healing of erosive oesophagitis. Previous studies have also confirmed the superiority of PPIs in maintaining healing of oesophagitis over H_2Ras (Sharma, 2003).

2.4.1.2 Oesophageal ulcers

Oesophagitis may cause oesophageal bleeding or ulcers. Ulcerations are excavated defects in the oesophageal mucosa that result when epithelial cells succumb to the caustic effects of refluxed acid and pepsin (Spechler, 2003). Oesophageal ulcers are complicated by hemorrhage, perforation, and penetration into the airway. Oesophageal ulcers can stimulate fibrous tissue production and collagen deposition that result in stricture formation, and the

ulcers can heal through a metaplastic process in which an intestinal-type epithelium replaces the damaged squamous cells (Barrett oesophagus) (Spechler, 2003).

2.4.1.3 Oesophageal strictures

A stricture is formed when oesophageal mucosal damage extends through the muscular layer, resulting in fibrosis. The classic presentation of a benign oesophageal stricture is slowly progressive dysphagia following long-standing symptoms of GORD. Subjects with stricture may need a biopsy to detect malignant lesions. Oesophageal ulcers can stimulate fibrous tissue production and collagen deposition that result in stricture formation (Spechler, 2003). nti-reflux therapy has been shown to reduce the need for recurrent dilation from oesophageal stricture formation (National Guideline Clearinghouse, 2002). Subjects with strictures on an initial endoscopic examination will need follow-up to evaluate the presence of underlying Barrett's oesophagus that may have been missed on the initial examination. This can occur when the presence of mucosal erosions/ulcerations obscures the identification of underlying Barrett's disease (Fennerty, 2003).

2.4.1.4 Barrett's oesophagus

Barrett's oesophagus is recognized as the most serious complication of gastro-oesophageal reflux disease (GORD) and a precursor of oesophageal adenocarcinoma. Barrett's oesophagus is defined as intestinal metaplasia of the oesophagus. The diagnosis of Barrett's depends upon a histologic examination, with the finding of intestinal goblet cells in the oesophageal biopsies. Although the diagnosis is made histologically, one must have a high index of suspicion for Barrett's oesophagus in subjects with a long history of reflux symptoms (Schneider, 2002). Some subjects that have suffered with heartburn find that the heartburn has become less severe or has disappeared over the recent months or years. This is because subjects with Barrett's oesophagus often loose their sensitivity to acid and bile reflux, probably on the basis of damage to sensory nerves in the oesophageal mucosa (Schneider, 2002).

Barrett's oesophagus is predominantly a disease of white males (Gopal, 2001; Cameron, 1992; Schneider, 2005). The mean age of development of Barrett's oesophagus is estimated to be 40 years, yet the mean age at diagnosis is 63 years. This suggests that a premalignant disorder may be present for up to 20 years before it is clinically recognized (Gopal, 2001).

Barrett's oesophagus is found in about 12% of subjects undergoing endoscopy for symptoms of GORD (Gopal, 2001). Certain subjects need to be screened for Barrett's oesophagus. Subjects who have had GORD symptoms for 5 years or longer have a markedly increased incidence of Barrett's oesophagus and oesophageal adenocarcinoma (Gopal, 2001).

Early endoscopic screening and surveillance is vital in subjects with Barrett's oesophagus and oesophageal adenocarcinoma. The aim of endoscopic screening and surveillance is to both identify Barrett's oesophagus and detect early dysplasia. The goal of such monitoring is to detect oesophageal cancer early, at a curable stage (Falk, 1999). Surveillance every 2 to 3 years is considered adequate for subjects who have no evidence of dysplasia (Sampliner, 1998). When low-grade dysplasia is present, the interval is shortened to every 6 months for 1 year, followed by annual surveillance. If high-grade dysplasia is detected on biopsy, an expert histopathologist should confirm the findings. When the confirmation is consistent with high-grade dysplasia, surveillance every 3 months is appropriate (Gopal, 2001; Valdivia and Fogel 2003).

2.4.1.5 Oesophageal adenocarcinoma

Intestinal metaplasia of the oesophagus is the premalignant lesion for adenocarcinoma of the oesophagus. Adenocarcinoma arises in a columnar lined or Barrett's oesophagus (Schneider, 2005). The risk of adenocarcinoma in subjects with Barrett's oesophagus is about 0.5% a year (Schneider, 2005). In subjects with severe reflux of more than 20 years duration, a 44-fold increased risk oesophageal adenocarcinoma is reported (Schneider, 2002; Lagergren, 1999). The significance of Barrett's oesophagus is that it is a pre-malignant condition leading, in some individuals, to adenocarcinoma of the oesophagus (Schneider, 2002; Reynolds, 1999). This is a devastating complication, as these subjects often present late in the course of the illness, making surgical cure impossible. In the patient with Barrett's oesophagus, a surveillance program is advised, with periodic endoscopic examinations being performed to detect dysplasia. The presence of high-grade dysplasia would require intervention (Schneider, 2002).

2.4.2 Extra-Oesophageal Complications

2.4.2.1 GORD and Asthma

In China, Jiang et al., (2005) proposed 2 mechanisms by which GORD might induce or aggravate asthmatic symptoms. One of the mechanisms was acid in the inflamed oesophagus acting on exposed receptors thereby stimulating bronchial hyper-responsiveness via the vagal reflex; or secondly micro-aspiration of gastric contents which damage the br nchial mucosa, resulting in inflammation of the mucosa and bronchial hyper-responsiveness.

Of the 15 million persons in the United States with asthma, 50% to 80% may also have GORD (Vaezi, 2005). Most subjects with asthma complain of coexisting heartburn and up to 75% of subjects have excess oesophageal acid exposure by pH monitoring (Harding, 2003). The cause-and-effect relationship between asthma and GORD has not been established since either condition may induce the other. Asthma attacks can cause oesophageal reflux of gastric contents by creating a negative intrathoracic pressure, overcoming the lower oesophageal sphincter barrier (Harding, 2003). Alternatively, gastro-oesophageal reflux either by direct aspiration or indirectly by stimulating the distal oesophageal sensory vagal nerve may induce bronchospasm and asthma (Vaezi, 2005). Additionally, it is recognized that asthma medications may promote GORD. Theophylline, beta-2 agonists, and even prednisone may increase oesophageal exposure to acid reflux by affecting protective mechanisms against GORD (Lazenby et al., 2002).

2.4.2.2 Dental Problems

Dental erosion is a very common problem in GORD subjects due to the acid backing up into the mouth and corroding tooth enamel.

2.4.2.3 Chronic cough

When subjects with chronic cough have prominent gastro-oesophageal symptoms consistent with GORD, reflux should be suspected, and a trial of antireflux therapy may be instituted without further diagnostic testing. Disappearance of the cough is required to confirm the diagnosis. GORD is one of most common causes of chronic cough in all age groups (Vaezi, 2005; Irwin, 2000).

2.4.2.4 Acid laryngitis

There is increasing evidence that GORD may be associated with chronic laryngeal signs and symptoms (Vaezi, et al., 2003). Laryngeal symptoms often associated with GORD may include hoarseness, throat clearing, cough, sore or burning throat and dysphagia (Vaezi, 2005). The most common mechanism for laryngeal irritation due to GORD is via direct contact with the gastroduodenal contents (Vaezi, et al., 2003). Recent studies show that pepsin and conjugated bile acids in acidic pH ranges result in laryngeal tissue inflammation, whereas nonacid exposure of any gastroduodenal agents does not cause injury (Adhami, et al., 2004).

2.4.2.5 Recurrent pneumonia

People with GORD appear to have an increased risk for recurrent pneumonia. If a person inhales fluid from the oesophagus (aspirates) into the lungs, serious pneumonia can occur. It is not yet known whether treatment of GORD would also reduce the risk for these respiratory conditions (Simon, 2002).

2.4.2.6 Non-cardiac chest pain (NCCP)

GORD may be the most common cause of non-cardiac chest pain. Recent data suggest that GORD may account for symptoms in 25% to 55% of subjects with non-cardiac chest pain. Direct contact of the oesophageal mucosa with gastroduodenal agents such as acid and pepsin is the most likely cause of these symptoms (Vaezi, 2005; Richter, 2000).

Initially, it may be difficult to distinguish GORD-related chest pain from angina. GORD-related chest pain can be squeezing or burning in nature, substernal in location, and may radiate to the back, neck, jaws, or arms. The pain may be worse after meals and disturb sleeping patterns. Exercise may induce GORD, resulting in chest pain, which can be indistinguishable from chest pain due to coronary disease. Symptoms may last for minutes or hours and are often relieved by antacids or acid-suppressive agents. It is imperative that the clinician rules out angina before considering GORD-related chest pain (Vaezi, 2005).

2.5 Diagnosis of GORD

Commonly employed diagnostic tests for the detection of GORD include barium swallow, gastroscopy, and 24-hour pH monitoring. However, based on a patient's history, empiric therapy is usually initiated prior to testing (Vaezi, 2005; Devault and Castell, 1999). Testing is usually indicated in subjects with persistent symptoms despite therapy, those with warning signs (i.e. dysphagia, weight loss, bleeding) or in those subjects with long-standing GORD in order to rule out Barrett's oesophagus (Vaezi, 2005).

According to the NICE guidelines (GC017), routine endoscopic investigation of subjects of any age, presenting with dyspepsia and without alarm signs (chronic gastrointestinal bleeding; progressive unintentional weight loss; progressive difficulty swallowing; persistent vomiting; iron deficiency anaemia; epigastric mass or suspicious barium meal), is not necessary. However, in subjects aged 55 years and older with unexplained and persistent recent-onset dyspepsia alone, an urgent referral for endoscopy should be made.

If oesophagitis is observed, documented grading systems allow specific definitions of its severity. The Savary-Miller grading system (I-IV) and Los Angeles grades A to D are commonly applied (Appendix 7). Barrett's oesophagus can be confirmed from biopsies showing the typical gastric columnar epithelium. The risk of developing carcinoma of the oesophagus increases with the length of segment of Barrett's mucosa (Kinnear, et al., 1999; Navaratnam and Winslet, 1998). Ambulatory pH monitoring may be necessary to diagnose endoscopy-negative subjects who respond poorly to treatment.

2.6 Lifestyle modifications

- Stop smoking
- Avoid alcohol
- Avoid lying down for 3 hours following a meal
- Avoid tight fitting clothes
- Elevate the head of the bed

2.7 Dietary modifications

- Weight loss
- Avoid large meals
- Avoid fatty, greasy food, or food containing caffeine
- Avoid chocolate
- Avoid caffeinated products
- Avoid tomato-based products
- Avoid spicy foods
- Avoid peppermint
- Avoid citrus fruits and juices

2.8 Medication to avoid

The following medication should be limited or avoided (Nice Guideline GC017):

- Calcium antagonists
- Nitrates
- Theophyllines
- Bisphosphonates
- Corticosteroids
- Non-steroidal anti-inflammatory drugs [NSAIDs]

2.9 Non-Erosive Oesophageal Reflux Disease

Symptoms of GORD can occur without any signs of inflammation or injury to the oesophagus. This condition is referred to as non-erosive oesophageal reflux disease (NERD). NERD rarely progresses to GORD. In NERD, subjects have no signs of inflammation or erosion in the oesophagus, but they experience certain symptoms of GORD, such as burning sensations behind the breastbone for at least three months (Simon, 2002). Researchers suggest that nerves lying near the surface of the lining become exposed to acid that has penetrated the layers. The nerves then trigger prolonged and painful symptoms in response (Simon, 2002).

2.10 Drug Treatment

The use of pharmacological agents to suppress gastric acid is the primary approach for reducing reflux symptoms, healing oesophagitis and maintaining remission. Clinical data indicate that oesophageal healing is influenced by both the degree and duration of gastric acid suppression. Healing rates increase in relation to the length of time that the intragastric pH remains above 4 (Scott, 1999; Howden, 1997). The agents used in treatment of GORD include antacids, scheduled H_2-receptor antagonists (H_2RAs), prokinetic agents and proton pump inhibitors (PPIs).

Table 1: Drugs used to treat GORD

Drugs	**Indications**
Antacids	Treatment for mild or infrequent symptoms of GORD
Histamine receptor blockers (H_2RAs)	Treatment of endoscopy-negative GORD and GORD with mild to moderate symptoms
ranitidine	
cimetidine	
Proton pump inhibitors (PPIs)	Treatment of GORD
pantoprazole	
esomeprazole	
rebeprazole	
omeprazole	
lansoprazole	
Prokinetic agents	Treatment of GORD
metoclopramide	
bethanechol	
Sucralfate	Treatment of GORD

Proton-pump inhibitors form the cornerstone of treatment for erosive oesophagitis and have been documented to be superior to H_2-receptor antagonists in meta-analyses for the healing of erosive oesophagitis. Previous studies have also confirmed the superiority of PPIs in maintaining healing of oesophagitis over H_2RAs (Sharma, 2003; Richter et al., 2003; Donnellan, 2003).

According to the NICE guidelines (2000/022), subjects who have severe gastro-oesophageal reflux disorder (GORD) symptoms or who have a proven pathology (e.g. oesophageal ulceration, Barrett's oesophagus) should be treated with a healing (high) dose of a PPI until symptoms have been controlled. After that has been achieved, the dose should be stepped down to the lowest dose that maintains control of symptoms. A regular maintenance low dose of most PPIs will prevent recurrent GORD symptoms in 70-80% of subjects and should be used in preference to the higher healing dose. Where necessary, should symptoms re-appear, the higher dose should be recommenced (appendix 1). In complicated oesophagitis (stricture, ulcer, haemorrhage), the full dose should be maintained. Subjects with mild GORD symptoms and/or those who do not have a proven pathology can frequently be managed by antacids, alginates, or H_2RAs.

2.10.1 Proton pump inhibitors

2.10.1.1 Pathophysiology

The parietal cells predominantly produce acid. Parietal cells contain receptors for three substances that stimulate acid production. These three substances are acetylcholine (ACh), gastrin, and histamine (appendix 9). Vagal stimulation via ACh release, the endocrine stimulation via gastrin release and the paracrine stimulation by local release of histamine result in acid secretion. The release of either ACh or gastrin also further stimulates histamine release. Activation of parietal H_2 receptors stimulates the cyclic adenosine 3,5 monophosphate (cAMP)-dependent pathway. The activation of muscarinic and gastrin receptors both result in the stimulation of the calcium (Ca^{2+})-dependent pathway. Stimulation of cAMP- and Ca^{2+}-dependent pathways results in the activation of the hydrogen/potassium adenosine triphosphate (ATPase) pump (Annis, 2003).

Once activated, the ATPase pump, also referred to as the proton pump, exchanges a hydrogen ion for a potassium ion at the secretory canaliculi. H_2RAs inhibit only the cAMP-dependent pathway from activating the proton pump, leaving the Ca^{2+}-dependent pathway open. PPIs block the proton pump and thus acid secretion from parietal cells, resulting in more complete acid suppression (Annis, 2003).

2.10.1.2 Pharmacology

PPIs are substituted benzimidazoles and are generally administered as tablets or capsules that pass through the stomach intact and are absorbed in the proximal small bowel. Once absorbed, all PPIs have a relatively short plasma half-life (about one to two hours). Their duration of action is much longer because of their unique mechanism of action. PPIs are lipophilic weak bases that cross the parietal cell membrane and enter the acidic parietal cell canaliculus. In this acidic environment, the PPI becomes protonated, producing the activated sulphonamide form of the drug that binds covalently with the H^+/K^+ ATPase enzyme that results in irreversible inhibition of acid secretion by the proton pump (Welage and Berardi, 2000). The parietal cells must then produce new proton pumps or activate resting pumps to resume acid secretion (Vanderhoff and Tahboub, 2002; Welage and Berardi, 2000).

PPIs block up to 80% of active proton pumps. In order to secrete more acid, parietal cells must either synthesize new proton pumps or activate resting pumps. Synthesizing new proton pumps takes 36 to 96 hours. Maximal intragastric pH control occurs when PPIs are taken 30 minutes before meals when more proton pumps are active. Since all proton pumps will not be active at any given time, a single dose of a PPI will not completely inhibit all acid secretion (Annis, 2003; Katz, 2005).

2.10.1.3 Pharmacokinetic parameters of PPIs

Table 2: Pharmacokinetic parameters of PPIs

Parameter	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Bioavailability	90%	80%-85%	30%-40%	77%	52%
Formulation	Capsule	Capsule	Capsule/Tablets	Tablet	Tablet
Time to peak plasma concentration	1.5 hours	1.7 hours	0.5-3.5 hours	2.5 hours	2-5 hours
Half-life (plasma)	1.2-1.5 hours	1.5 hours	0.5-1 hour	1 hour	1-2 hours
Major cytochrome P450 pathway	CYP2C19	CYP3A, CYP2C19	CYP2C19	CYP2C19	CYP3A CYP2C19
Protein binding	97%	97%	95%	98%	96.3%

(Annis, 2003; Vanderhoff and Tahboub, 2002)(Information compiled from package inserts)

2.10.1.4 Adverse effects

The frequency of adverse effects associated with PPIs is similar to that of placebo, with an overall incidence of less than 5 percent (Reilly, 1999). The type and frequency of adverse effects are similar to those observed with histamine H_2-receptor blockers. The most common adverse effects are headache, diarrhoea, abdominal pain, and nausea (Vanderhoff and Tahboub, 2002). There has been a report of loss of libido in 1 subject during treatment with esomeprazole (Rosenshein, et al., 2004). However no other cases like this have been subsequently reported.

PPIs are contraindicated in subjects with known hypersensitivity to any component of the PPI formulation. Long-term safety with the use of PPIs has been a concern, although no data

exist to support these concerns. With no increase in adverse effects and with insufficient data to support claims of increased risk of cancer or atrophic gastritis, the long-term use of PPIs appears to be safe (Annis, 2003).

2.10.1.5 Drug Interactions

PPIs cause significant increases in gastric pH, which may alter the absorption of weak acids or bases. Coadministration with these agents should be approached cautiously because it may result in clinical treatment failure (Welage, 2000). PPIs are metabolized to varying degrees by the hepatic cytochrome P450 enzymatic system and may alter drug metabolism by induction or inhibition of the cytochrome P enzymes (Welage, 2000; Reilly, 1999). This is an important consideration in subjects taking medications with a narrow therapeutic window (Vanderhoff And Tahboub, 2002).

2.10.1.6 PPI drug interactions.

Table 3: Important PPI drug interactions.

Drug	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Carbamazepine	↓Metabolism	Unknown	↓Metabolism	None	Unknown
Diazepam	↓Metabolism	None	↓Metabolism	None	None
Digoxin	↑Absorption	Unknown	↑Absorption	↑Absorption	↑Absorption
Ketoconazole	↓Absorption	↓Absorption	↓Absorption	Unknown	↓Absorption
Methotrexate	↓Renal excretion	Unknown	↓Renal excretion	Unknown	Unknown
Nifedipine	↑Absorption	Unknown	↑Absorption	↑Absorption	Unknown
Oral contraceptives	None	None	None	None	Unknown
Phenytoin	↓Metabolism	None	↓Metabolism	None	None
Theophylline	None	↑Metabolism	None	None	None
Warfarin	↓Metabolism	None	↓Metabolism	None	None

(Annis, 2003; Vanderhoff And Tahboub, 2002) (Information compiled from package inserts)

2.10.1.7 Indications

All PPIs share a common mechanism of action. While they may differ in terms of their pharmacokinetic profile the end result is the same, namely suppression of acid secretion.

2.10.1.8 PPI dosage

Table 4: PPI dosing regimens

Indication	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Healing erosive oesophagitis	20-40 mg D x 4-8 weeks	30 mg D up to 8 weeks*	20 mg D x 4-8 weeks	40 mg D up to 8 weeks*	20 mg D x 4-8 weeks
Maintenance of erosive oesophagitis	20 mg D	15 mg D	20 mg D	40 mg D	20 mg D
Symptomatic GORD	20 mg D x 4 weeks**	15 mg D up to 8 weeks	20 mg D x 4 weeks**		

D = once daily

*In subjects who have not healed after eight weeks of therapy, an additional eight weeks of treatment may be considered.

**If symptoms do not resolve completely after four weeks, an additional four weeks of treatment may be considered.

(Annis, 2003; Meyer, 2001) (Information compiled from package inserts)

The goal of treatment for GORD is to relieve symptoms and prevent further symptoms and complications from occurring. The degree of acid suppression controls the symptoms of GORD and healing of erosive oesophagitis. There are two main approaches in the treatment of uncomplicated GORD, the use of over the counter (OTC) (antacids and H_2RAs) products and the use of PPIs (Annis, 2003; Meyer, 2001).

The American Gastroenterological Association (AGA) recommends H_2RAs for the treatment of endoscopy-negative GORD and GORD with mild to moderate symptoms. PPIs have shown superiority in healing of erosive oesophagitis over placebo and H_2RAs. AGA recommends the use of PPIs in subjects with severe symptoms, who fail H_2RA therapy and with endoscopy-positive GORD. PPIs are the most effective drugs available to provide rapid oesophageal healing and symptom relief. Higher doses or longer duration of therapy may be

required in severe cases. When deciding whether to initiate traditional OTC therapy or PPI therapy without an endoscopy, the provider should take into consideration the patient's insurance coverage, ability to pay and severity of symptoms (Annis, 2003).

2.10.1.9 Comparison of different PPIs

According to direct comparative trials of PPIs by Vakil and Fennerty (2003), pharmacological differences are relevant only if there are clinically important differences in efficacy, tolerability or safety of the compounds. There have been few head-to-head trials measuring clinically meaningful outcomes to prove potential differences in therapeutic efficacy. This has led some to compare the clinical outcomes of individual proton pump inhibitors across separate trials. This form of comparison is inappropriate because differences in study design and population may bias the outcomes. Thus, only head-to-head studies are appropriate for determining whether clinical differences exist (Vakil and Fennerty, 2003). Thirty-two trials were analysed in the study by Vakil and Fennerty.

2.11 Overview of literature survey

GORD is considered to be to a lifestyle disorder. Whilst this is true in most subjects, there are a percentage of subjects who have complications of GORD as well as alarming symptoms. It is in these subjects that GORD is no longer just a lifestyle disorder. The complications of GORD can lead to serious consequences if not diagnosed timeously. Gastroscopy is an objective criterion in diagnosing these complications and its value should not be under-estimated.

The alarming symptoms of GORD are dysphagia, non-cardiac chest pain, GI bleeding, anaemia, choking and unexplained weight loss. The most common symptoms of GORD are heartburn and regurgitation. Oesophageal symptoms of GORD include Barrett's oesophagus, oesophageal stricture, oesophageal ulcer, oesophageal erosions and oesophageal adenocarcinoma.

In a small percentage of chronic subjects, a serious form of GORD called Barrett's oesophagus may eventually develop, in which erosion can lead to cancerous changes in the tissue lining of the oesophagus. Oesophageal stricture can be a major concern as it can be the result of long-term oesophagitis resulting in fibrosis of the lower oesophagus or oesophageal

adenocarcinoma. An oesophageal ulcer is also a severe form of oesophagitis. This is most frequently seen in a patient with long-term erosive oesophagitis. It is important to identify and treat these subjects as the ulcer may erode through the oesophagus causing oesophageal perforation. A small percentage of subjects with GORD will have oesophageal bleeding. Subjects with symptoms of dysphagia and more extensive Barrett's oesophagus have a further increased risk, and gastroscopy with biopsy should be repeated at least yearly. The prognosis in these subjects may be grim. It is in these subjects with complications of GORD where the use of the gastroscopy is of utmost importance (Falk, 1999).

Empirical therapy is the most cost effective way of treating subjects without alarming symptoms. In most cases it is unnecessary to perform a gastroscopy in these subjects. Most of the symptoms in these subjects resolve after 1-2 months of treatment. Many subjects are unnecessarily treated for longer periods of time thus increasing costs. The subjects with complications of GORD as well as alarming symptoms need to have a gastroscopy performed. This helps identify subjects with complications timeously and avoids, delays or stops the progression of the complications of GORD.

According to the NICE guidelines, routine endoscopic investigation of subjects, presenting with dyspepsia and without alarming symptoms, is not necessary. However, for subjects with complications or alarming symptoms, gastroscopy should be considered. The NICE guidelines also recommend 1-2 months of full dose proton pump inhibitor in a subject presenting with dyspepsia and without alarming symptoms (CG017NICE guideline).

Medical aid societies currently request a gastroscopy for subjects applying for chronic authorisation for GORD treatment. However, this practise should be changed to a more cost effective approach. It would be more economical and therapeutically effective if the subjects without complications of GORD and without alarming symptoms were given an empirical trial of PPIs. Only if symptoms do not resolve or if subjects have complications or alarming symptoms, then only should a gastroscopy be done. This could result in a phenomenal cost saving. In this retrospective study, 74% of subjects that had a gastroscopy performed, did not have complication. If these subjects did not have any alarming symptoms and therefore did not require a gastroscopy, there could have been a huge cost saving. Subjects without alarming symptoms and complications could have been treated for a shorter period of time.

Subjects without alarming symptoms should be treated empirically for 1-2 months, however if symptoms do not resolve or if subjects have complications, then only should a gastroscopy be performed.

CHAPTER THREE: METHODOLOGY

3.1 Study Design

This study is a retrospective analysis of subjects diagnosed for the first time with gastro-oesophageal reflux disease (GORD) at a private medical aid namely, National Medical Plan (NMP), for the period 1st January 2002 to 31st December 2003.

3.2 Subject selection

The medical records (from the database of NMP) of all newly diagnosed subjects with GORD, with or without gastroscopy, were reviewed for the period January 2002 to December 2003. The study population comprised of South Africans of African decent, Coloureds, Asians, and Whites.

3.3 Study procedure

Data requested from the Information Technology (IT) department of NMP included the following:

- The number of all current, active subjects diagnosed with GORD
- The age/race/sex of subject
- The number of gastroscopies (gr) performed on each subject within the time frame under review
- The number of subjects that did not have gastroscopy within the study period
- History of concurrent illnesses
- History of medication for GORD and concurrent illnesses
- Complications of GORD
- The duration of GORD treatment
- The cost of drug therapy with or without gastroscopy
- The cost of gastroscopy

3.4 Inclusion criteria

- Compliant subjects
- Newly diagnosed
- Continuous treatment for GORD

- On current treatment for GORD
- No previous treatment for GORD

3.5 Exclusion criteria

- Previous treatment for GORD
- Intermittent treatment for GORD
- Non-compliant subject
- Subjects who died (cause of death was non-GORD related)

3.6 Data collection and Statistical analysis

Data was collected via a business objective report from the Information Technology Department from the private medical aid administrator. This information was captured on Microsoft Excel®. Results obtained in the 2 groups (with and without gastroscopy) were compared using the chi-squared statistical test. Data was summarised using percentages to populate tables and graphs. All tests with a p value less than 0.001 was considered significant. Data analysis was completed in consultation with a biostatistician from the Medical Research Council, Durban, Kwazulu-Natal, South Africa.

3.7 Medico-legal consideration

Ethical clearance was obtained from the University of Kwazulu-Natal (appendix 4). Permission to access medical aid information was obtained from National Medical Plan (NMP) (appendix 5). Subject details were coded so that confidentiality was maintained. No reference to any individual subject was made in the text.

CHAPTER FOUR: RESULTS AND DISCUSSION

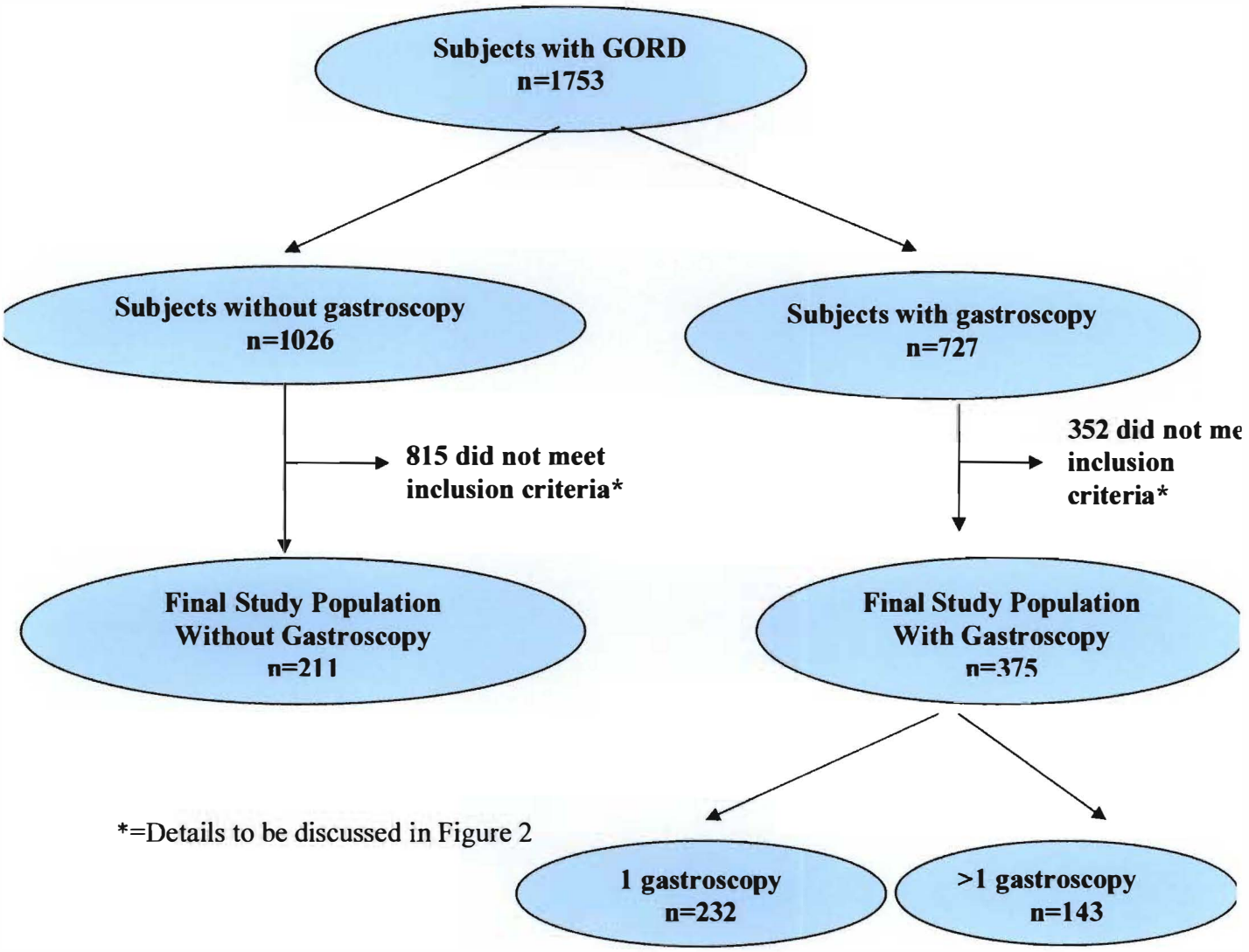

Figure 1: Schematic representation of selection of subjects of the study cohort

The study population was identified as presented in figure 1. One thousand seven hundred and fifty three subjects with GORD were identified. Two subsets of subjects were identified. One subset did not have a gastroscopy done (59%; *n*=1026) (these subjects were treated depending on the clinical evaluation of the attending doctor). Eight hundred and fifteen subjects without gastroscopy did not meet the inclusion criteria. Hence the final study population without gastroscopy was 211. The second subset comprised subjects that had a gastroscopy done (41%) (*n*=727). Three hundred and fifty two subjects with gastroscopy did not meet the inclusion criteria. The final study population with gastroscopy was 375. These

subjects were further identified as those that had one (n=232) or more than one gastroscopy done (n=143).

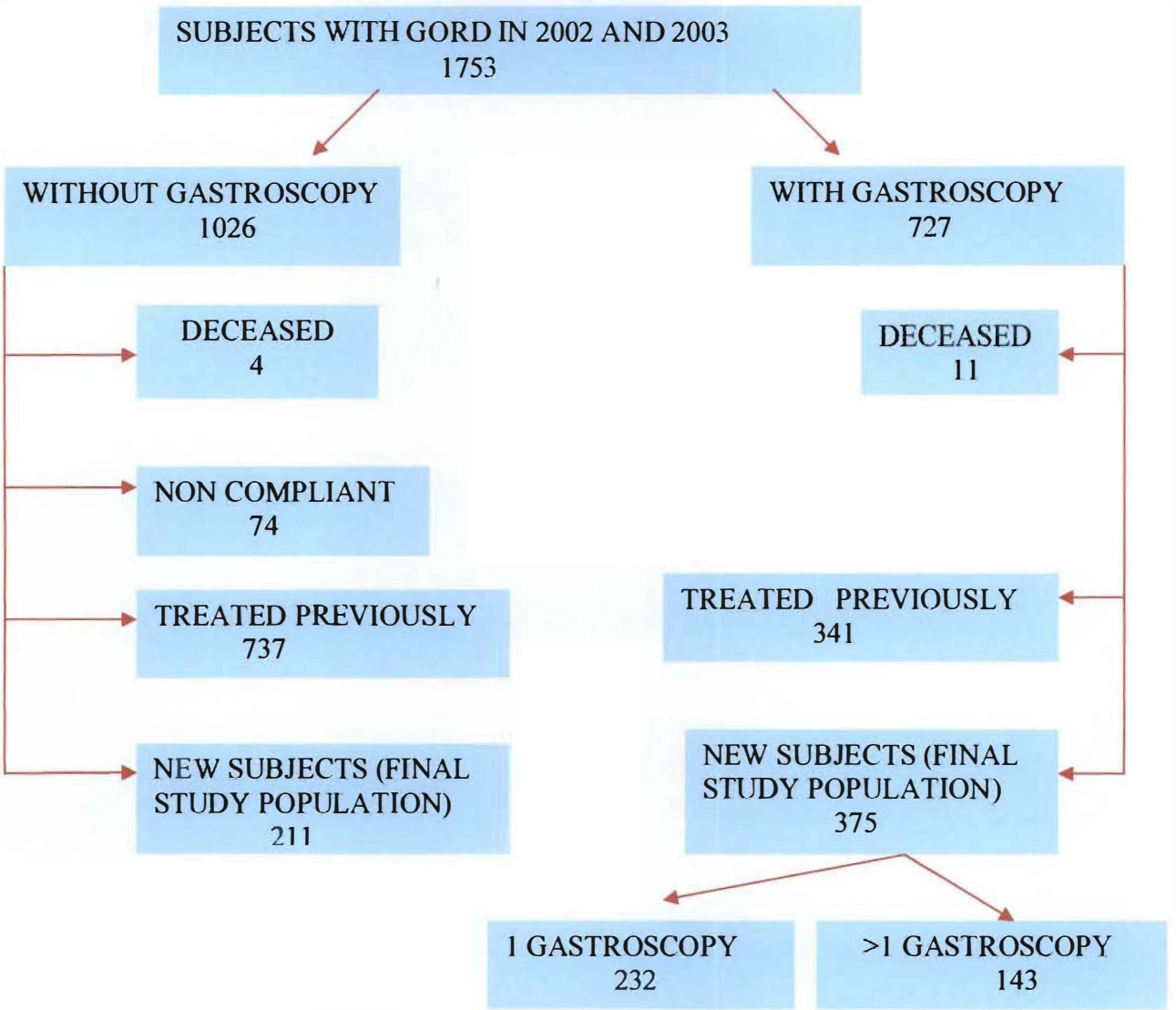

Figure 2: Schematic representation of exclusion and selection of subjects of the study cohort

In the subset with gastroscopy, 11 subjects were deceased (non-GORD related), 341 were previously treated for GORD and 375 were newly diagnosed subjects. The 375 new subjects with gastroscopy were further grouped into subjects with 1 gastroscopy or more than 1 gastroscopy. In the subset without gastroscopy, 4 subjects were deceased (non-GORD related), 737 were previously treated for GORD, 74 were non-compliant and 211 were newly diagnosed subjects.

The newly diagnosed subjects with gastroscopy (n=375) and without gastroscopy (n=211) satisfied the inclusion criteria. The cause of death in subjects who died was non-GORD related medical conditions and these subjects did not have any complications of GORD.

4.1 Demographics

Table 5: Demographics

Variable		Subjects without gastroscopy % *(n=211)*	Subject with gastroscopy % *(n=375)*	p value
Sex	Male	48.8% (103)	52.3%(198)	0.4
	Female	51.2% (108)	46.9%(177)	n.s.
Age	>55 years	55.5%(117)	60.3%(226)	0.26
	<55 years	44.5%(94)	39.7%(149)	n.s.
Ethnicity	African	1.4%(3)	1%(4)	0.8 n.s.
	Coloured	0(0)	0%(1)	
	Indian	17.5%(37)	19.9%(71)	
	White	81%(171)	79.7%(299)	
Total		211	375	-

n.s.=not significant

Table 5 is a synopsis of the demographics of the study population. Of the 586 subjects who satisfied the inclusion criteria, 211 did not have a gastroscopy and 375 had a gastroscopy performed. The 2 groups (with gastroscopy and without gastroscopy) were equally matched for sex, age and ethnicity. There was no statistically significant difference in the demographics of the population of subjects with or without gastroscopy. Hence comparisons are possible.

Of the subjects without gastroscopy, females comprised 51.2% (n=108) and in subjects with gastroscopy females comprised 46.9% (n=177). In the present study the male to female ratio was approximately 1:1 in the subjects without gastroscopy and 1: 0.9 in subjects with gastroscopy. In both study groups, the number of female and male subjects was evenly

matched. While there are no comparable published studies on GORD in South Africa, a study done in Finland found the male to female ratio to be 1:1.3 (Voutilainen, 2002).

The study population was categorised into the age groups, greater than and less than 55 years, utilising the NICE guidelines (GC017). Subjects >55 years without gastroscopy comprised 55.5% (*n*=117) and subjects with gastroscopy comprised 60.3% (*n*=226) of the study population. Subjects < 55 years without gastroscopy and subjects with gastroscopy comprised 44.5% (*n*=94) and 39.7% (*n*=149) of the study population respectively. In both study groups, there were more subjects with GORD in the age group >55 years. This compares favourably to the study conducted in Finland (Voutilainen, 2002) where the mean age of subjects were 58.1 years. The mean age of the subjects with and without gastroscopy in this study was 58.3 and 56.3 years respectively. There are no comparable published studies on GORD in South Africa to make comparisons.

Potential factors aggravating GORD in the elderly include concurrent medication which may reduce lower oesophageal sphincter pressure, increase the frequency of hiatal hernia, impair gastro intestinal motility and decrease saliva volume (Voutilainen, 2002). Community studies have identified associations between GORD symptoms and age (Isolau i and Laippala, 1995). This was seen in this study, where more subjects with GORD were >55years. According to the NICE guidelines (NGC017) recommendations, in subjects aged 55 years and older with unexplained and persistent recent-onset dyspepsia alone, an urgent referral for endoscopy should be made.

The subset without gastroscopy comprised of 81% white subjects (*n*=171), 17.5% Indian subjects (*n*=37) and 1.4% Af ican subjects (*n*=3). The subset with gastroscopy comprised 79.7% white subjects (*n*=299), 19.9% Indian subjects (*n*= 71) and 1% African subjects (*n*=4).

The prevalence of GORD in this study was found to be highest amongst the white population. Since the data was taken from a medical aid fund, data could have been skewed towards the more affluent white society. African, Indians and Coloured are economically disadvantaged and therefore less likely to belong to a medical aid. However, international studies show that GORD occurs more frequently in white subjects rather than African subjects (Spechler, 2002). It would appear that GORD is detected more frequently in the economically advantaged communities and in urban areas due to better access to medical

care rather than race *per se* . Complicated gastro-oesophageal reflux disease appears to be predominantly a disorder of whites (Spechler, 2002).

A study conducted at Chris Hani Baragwanath Hospital concluded that urbanization had increased the risk associated with the development of GORD in blacks (Segal, 2001). However, one would have expected this to lead to an increase in this disease among Africans, but this increase has not occurred (Segal, 2001). Although urbanization has increased the prevalence of GORD as reflected in the Baragwanath study, this has not translated to an increase in GORD in this study of African subjects. The significance of this finding is that this study reflects GORD in an economically advantaged community which cannot be extrapolated nationally. Therefore, it is recommended that similar studies be conducted nationally in both the private and public sectors to give a more accurate reflection of the demographics of the disease.

4.2 Medical Conditions

4.2.1 Concurrent Medical Conditions

There were 82 concurrent medical conditions other than GORD identified in this study population. (Appendix 2) .The 2 subsets of subjects had 52.4% *(n*=43) common concurrent medical conditions. The subset without gastroscopy had an additional 12.2% *(n*=10) concurrent diagnoses and the subset with gastroscopy had an additional 35.4% *(n*=29) concurrent diagnosis. Concurrent medical conditions were evaluated as the 10 most common conditions and further subdivided as directly related, indirectly related and unrelated concurrent medical conditions. The top 10 diagnoses were the most commonly occurring concurrent diagnosis amongst the study population.

Table 6: Top 10 concurrent medical conditions identified for the study population

Medical conditions	Subjects without gastroscopy % (*n*)	Subjects with gastroscopy % (*n*)	Total % (*n*)
Hypertension	31.8 (67)	43.7 (164)	38.8 (231)
Hyperlipidaemia	25.1 (53)	24.8 (93)	24.5 (146)
Menopause	24.6 (52)	23.7 (89)	23.7 (141)
Depressive episode	16.5 (37)	17.3 (65)	17.1 (102)
*Osteoporosis	10.9 (23)	10.4 (39)	14.4 (62)
*Osteoarthritis	9 (19)	9.6 (36)	9.2 (55)
*Asthma	9.5 (20)	8 (30)	8.4 (50)
Chronic ischaemic heart disease	10.9 (23)	6.9 (26)	8.2 (49)
Diabetes	10 (21)	7.2 (27)	8 (48)
Hypothyroidism	9 (19)	6.4 (24)	7.2 (43)

* indirectly related to GORD

(Subjects may have more than 1 concurrent diagnosis).

The top 10 medical conditions presented in this study are similar to the current top 10 medical conditions in South Africa (as per Medical Aid Fund Reports) (appendix 6). Of the top 10 most common concurrent medical conditions, 3 diagnoses were indirectly related to GORD and 7 were unrelated to GORD. The 3 diagnoses indirectly related to GORD were asthma (8.4%, *n*=50), osteoarthritis (9.2%, *n*=55) and osteoporosis (14.4%, *n*=62). In subjects without gastroscopy, the subjects with asthma, osteoarthritis and osteoporosis were 9.5% (*n*=20), 9% (*n*=19) and 10.9% (*n*=23) respectively. These diagnoses occurred in similar percentages in subjects with gastroscopy viz.8% (*n*=30) in asthma, 9.6% (*n*=36) in osteoarthritis and 10.4% (*n*=39) in osteoporosis. The diagnoses directly related to GORD were diaphragmatic hernia, anaemia and peptic ulcer. In subjects without gastroscopy, the subjects with diaphragmatic hernia, anaemia and peptic ulcer were 1.4% (*n*=3), 1.4% (*n*=3) and 0.9% (*n*=2) respectively. In subjects with gastroscopy, the subjects with diaphragmatic hernia, anaemia and peptic ulcer were 4.3% (*n*=16), 4% (*n*=15) and 0.5% (*n*=2) respectively.

The drug treatment used for these conditions (osteoarthritis, osteoporosis and asthma) irritate the gastric mucosa and worsen GORD. These medical conditions will be further discussed under directly and indirectly related concurrent medical conditions. Asthma itself is also inter-related with GORD. GORD is recognized as a potential trigger for asthma symptoms (Kiljander, 2003).

4.2.2 Directly Related Concurrent Medical Conditions

Table 7: Medical conditions directly related to GORD for the study population

Diagnosis	Subjects without gastroscopy % (*n*)	Subjects with gastroscopy % (*n*)	Total % (*n*)
Diaphragmatic hernia	1.4 (3)	4.3 (16)	3.2 (19)
Anaemia	1.4 (3)	4 (15)	3 (18)
Peptic ulcer	0.9 (2)	0.5 (2)	0.7 (4)

Table 7 lists the directly related concurrent medical conditions: diaphragmatic hernia, anaemia and peptic ulcer.

The directly related medical conditions associated with GORD are presented in table 7. **Diaphragmatic hernia** occurred in 1.4% (*n*=3) of subjects without gastroscopy and 4.3% (*n*=16) of subjects with gastroscopy. Gastroscopy detects complications in GORD subjects. Kahrilas (2001) (United States) reported that hiatus hernia is a significant pathophysiologic factor in 50% to 94% of subjects with GORD. Hiatal hernia displaces the LOS segment of the distal oesophagus, both reducing LOS pressure and impairing acid clearance (Richter, 1999). Once reflux has occurred, impaired acid clearance prolongs exposure of the mucosa to the damaging effects of the refluxate (Klinkenberg-Knol et al., 1995). Hiatus hernia thus promotes reflux of acid content, thereby contributing to GORD (Locke et al., 2003). The presence of GORD and diaphragmatic hernia concurrently can aggravate the symptoms of GORD if not treated timeously and appropriately. In this study, subjects with hernia were treated with PPIs.

Anaemia was found in 1.4% *(n*=3) of subjects without gastroscopy and 4% *(n*=15) of subjects with gastroscopy. Simon et al., (2002) in their study found bleeding to occur in over 8% of subjects with erosive oesophagitis (severe inflammation of the oesophagus), which is associated with GORD. In very severe cases, the subject may detect dark-coloured, tarry stools (indicating bleeding) or vomit blood, particularly if ulcers have developed in the oesophagus. This is a sign of severe damage and requires immediate attention. Sometimes long-term bleeding can result in iron deficiency anaemia and may sometimes even require emergency transfusions. This condition can occur without heartburn or other warning symptoms or even obvious blood in the stools.

Anaemia is one of the alarming symptoms of GORD (Valdivia and Fogel 2003). Subjects with oesophageal erosions present with anaemia and require treatment with iron supplements. A bleeding oesophageal ulcer with excessive blood loss can be fatal. Drugs used to treat anaemia for example iron supplements are also known to cause GORD (Simon, 2002).

Peptic ulcer disease (PUD) occurred in 0.9% *(n*=2) of subjects without gastroscopy and in 0.5% *(n*=2) of subjects with gastroscopy. Peptic ulcers develop when the lining of the stomach or duodenum is chronically inflamed or exposed to excess stomach acid and digestive enzymes. These disorders are usually caused by infection with the bacterium *Helicobacter pylori*, and use of drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs). Peptic ulcers can develop potentially life-threatening complications, such as penetration, perforation and bleeding. GORD is defined as chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the oesophagus. The high acidic content of the stomach secretions in PUD, refluxes into the oesophagus in subjects with GORD, thus aggravating GORD. This contributes to complications such as anaemia, oesophageal erosions and oesophageal ulcers.

Subjects with GORD and PUD who are on NSAIDS will need re-evaluation of their treatment. For subjects being treated for rheumatoid arthritis, the second line treatment after NSAID use is Disease Modifying Anti-Rheumatic Drugs (DMARDS) such as methotrexate. However, these drugs also cause gastric irritations. The next option could be the addition of a PPI to the treatment programme. The attending clinician may need to add on treatment appropriately.

4.2.3 Indirectly Related Concurrent Medical Conditions

Table 8: Concurrent medical conditions indirectly related to GORD for the study population

Diagnosis	Subjects without gastroscopy % (*n*)	Subjects with gastroscopy % (*n*)	Total % (*n*)
Osteoporosis	10.9 (23)	10.4 (39)	10.6 (62)
Osteoarthritis	9 (19)	9.6 (36)	9.4 (55)
Asthma	9.5 (20)	8 (30)	8.5 (50)
Rheumatoid arthritis	6.6 (14)	6.9 (26)	6.8 (40)
Angina pectoris	3.8 (8)	1.9 (7)	2.6 (15)
Soft tissue disorder	4.7 (1)	3.3 (7)	1.4 (8)
Neoplasm (breast and prostrate)	0.9 (2)	1.1 (4)	1 (6)

The indirectly related concurrent medical conditions identified were osteoporosis, osteoarthritis, asthma, rheumatoid arthritis, angina pectoris, soft tissue disorder and neoplasms.

Osteoporosis was present in 10.9% (*n*=23) of subjects without gastroscopy and 10.4% (*n*=39) with gastroscopy. It occurred in similar frequency in both the subsets. Alendronate (Fosamax®) is used for osteoporosis and is recognised for the direct damage it causes to the oesophageal mucosa (Kinnear et al., 1999). Alendronate was used in 5.2% (*n*=11) of subjects without gastroscopy and 3.7% (*n*=14) of subjects with gastroscopy. Subjects, who have GORD and osteoporosis and are being treated with alendronate, may need to investigate the use of an alternative drug, which does not cause damage to the gastric mucosa. This will be further discussed under concurrent drug treatment.

Osteoarthritis occurred in both population groups with a similar frequency, being 9% (*n*=19) of subjects without gastroscopy and 9.6% (*n*=36) of subjects with gastroscopy. These subjects were on NSAIDS therapy, which is known to induce gastric irritation. The other concurrent medical conditions such as soft tissue disorder, pain and myalgia also have an

indirect effect on GORD. This is due to the use of NSAIDS, which causes gastric mucosal irritations (Kinnear et al., 1999).

Asthma was present in 9.5% *(n*=20) of subjects without gastroscopy and 8% *(n*=30) of those with gastroscopy. According to Vaezi (2005), GORD may occur in as many as 50% to 80% of subjects with asthma. According to Kiljander (2003), GORD occurs in at least one third of subjects with asthma and is recognized as a potential trigger for asthma symptoms. In this study, both subsets had a lower frequency of GORD with asthma in comparison to the above-mentioned studies. Future studies on the prevalence of GORD in asthma subjects locally may need to be investigated. These studies could provide some insight into the inter-relationship between GORD and asthma so that this inter-relationship could be better managed.

In China, Jiang et al., (2005), proposed 2 mechanisms by which GORD might induce or aggravate asthmatic symptoms. One of the mechanisms was the presence of acid in the inflamed oesophagus acting on exposed receptor thereby stimulating bronchial hyper-responsiveness via the vagal reflex; or secondly, micro-aspiration of gastric contents which damage the bronchial mucosa, thereby resulting in inflammation of the mucosa and bronchial hyper-responsiveness.

According to Kiljander (2003), it does appear that PPI treatment may improve nocturnal asthma symptoms in subjects who also have GORD. Moreover, both daytime asthmatic symptoms and pulmonary function seem to improve in some subjects with PPI treatment (Kiljander, 2003). Medical or surgical treatment of GORD in children with asthma and documented GORD results in a significant reduction in the requirement for asthma medications (Barclay et al., 2003).

In this study population, **rheumatoid arthritis** occurred in 6.6% *(n*=14) of subjects without gastroscopy and 6.9% *(n*=26) of subjects with gastroscopy. Rheumatoid arthritis occurred in similar frequency in both the population groups. The drug treatment used for rheumatoid arthritis consists of non-steroidal anti-inflammatory drugs (NSAIDS), Disease Modifying Anti-Rheumatic Drugs (DMARDS) and corticosteroids. These drugs aggravate GORD.

NSAIDS cause gastrointestinal mucosal injury. Up to 100% of subjects taking nonselective NSAIDs will demonstrate sub-epithelial haemorrhage, about 50% will have erosions and

20% or more will have ulceration. Possible complications of ulcers are bleeding and perforation (Fennerty, 2001). Cessation of NSAID results in most ulcers healing spontaneously. If the NSAID cannot be discontinued, addition of a PPIs to the NSAID regimen heals the ulcer and maintains the healing in most subjects (Yeomans et al., 1998; Hawkey et al., 1998)

The specific cyclo-oxygenase-inhibitors (COXIB) were the drugs of choice in subjects who could not tolerate the NSAIDS. However COX 2 inhibitors increased the risk of cardiovascular events by causing an imbalance in the vascular compartment of prostaglandin production, with an excess of platelet thromboxane and therefore increased platelet aggregation (Berenbaum, 2005). Rofecoxib has been withdrawn from clinical use due to its adverse cardiac effects, e.g. myocardial infarction and cerebrovascular accidents. Berenbaum (2005) suggests that the adverse cardiac effects of COX 2 inhibitors may be a class effect implying that others in the class will not be safe to use. Meloxicam, a partially selective COX 2 inhibitor may also have the same adverse effects (FitzGerald, 2001; Fries, 2005). Currently lipoxins, a new class of drugs, which are in phase 2 trials, are expected to replace the COX inhibitors in subjects with gastric irritations (Souza et al., 2003).

For subjects with a documented NSAID-induced ulcer, and who must unavoidably continue with NSAID therapy (e.g. those with severe rheumatoid arthritis), an acid suppressor, usually a PPI should be co-prescribed. After the ulcer has healed, where possible, treatment should be stepped down to a maintenance dose of the acid suppressor (NICE 2000/022).

Angina pectoris occurred in 3.8% (*n*=8) of subjects without gastroscopy and in 1.9% (*n*=7) of those with gastroscopy. Subjects with recurrent angina-like chest pain with normal coronary vessels are deemed to have the syndrome of noncardiac chest pain (NCCP) (Shrestha et al., 2000). The proximity of the oesophagus to the heart and its shared visceral enervation are believed to be underlying factors. Pain is thought to occur as a result of stimulation of chemoreceptors or by oesophageal distention (Kahrilas, 2003). These recurrent episodes of chest pain may be related to GORD. Shrestha et al., (2000), estimates that approximately 44% of subjects with NCCP may have underlying GORD. Subjects with angina pectoris need to be investigated and treated appropriately with the necessary tests (ECG, cardiac enzymes) and medication. However, if after investigation the pain is found to be of non-cardiac origin, the subject needs to be educated regarding GORD and non-cardiac

chest pain. The subject needs to be aware of dietary changes, lifestyle adjustments and medication that will stop the NCCP.

Subjects with GORD and **neoplasm (breast and prostrate)** were 0.9% *(n*=2) in the subset without gastroscopy and 1.1% *(n*=4) for those with gastroscopy. The hormone inhibitors e.g. bicalutamide (*n*=1) (Casodex®) and anastrozole (*n*=2) (Arimidex®) used for treating neoplasms have severe gastro-intestinal side effects. According to the NICE guidelines (G 017), drugs causing irritation to stomach lining must be stopped or an alternative medication must be prescribed to relieve the dyspepsia symptoms. Since continuation of these medications is vital for treatment of neoplasms, additional medications to relieve the gastro-intestinal tract irritations (such as PPIs) need to be prescribed. Although this diagnosis occurred at a very low frequency, the significance of these serious complications should not be overlooked.

All other concurrent medical conditions are presented in appendix 2

4.3 Concurrent Drug Therapy

Table 9: Concurrent drug therapy for the study population

Concurrent Drug Therapy	Subjects without Gastroscopy % (*n*)	Subjects with Gastroscopy % (*n*)	p value
Greater than 3%			
NSAIDS	6.2 (13)	3.7 (14)	0.2
Calcium Channel Blockers	10 (21)	11.7 (44)	0.6
Iron Supplements	0.9 (2)	3.7 (14)	0.06
Aspirin	6.6 (14)	5.3 (20)	0.6
COXIB inhibitors	9.5 (20)	12.5 (47)	0.3
COX 2 inhibitors	4.3 (9)	3.5 (13)	0.7
Enteric coated aspirin	12.3 (26)	8.2 (31)	0.1
Alendronate	5.2 (11)	3.7 (14)	0.4
Warfarin	1.9 (4)	3.5 (13)	0.3
Less than 3%			
Sulphasalazine	0.9 (2)	1.3 (5)	0.9
Immunosupressants	0.5 (1)	1.1 (4)	0.7
Diclofenac/misoprostol combination	0.5 (1)	2.1 (8)	0.2
Theophylline	2.4 (5)	2.9 (11)	0.8
Corticosteroid	2.8 (6)	2.4 (9)	0.8
Methotrexate	1.4 (3)	1.1 (4)	0.7

See all concurrent drugs –appendix 3

Subjects were grouped into 2 categories, those that represented greater than and equal to 3% and those that represented less than and equal to 3%. This classification is an attempt to categorise the more important drugs likely to affect the disease. NSAIDS, calcium channel blockers, iron supplements, aspirin, COXIB inhibitor, COX II inhibitor, enteric coated aspirin, alendronate, warfarin fall into the category where the subjects number greater than or equal to 3%. Calcium channel blockers, bisphosphonates and NSAIDs have been mentioned

in the NICE guidelines (GC017) a possible causes of dyspepsia. Sulphasalazine, immunosupressants, diclofenac/misoprostol combination, theophylline, corticosteroid, methotrexate fall into the category where the subjects number less than or equal to 3%.

In this study population, **NSAIDS** were used in 6.2% *(n*=13) of the subjects with gastroscopy and 3.7% *(n*=14) of the subjects without gastroscopy. The frequency of NSAIDS use was lower in the subset with gastroscopy. These drugs are used for rheumatoid arthritis and osteoarthritis. As discussed previously, NSAIDS cause gastrointestinal mucosal injury thus aggravating GORD (Kinnear et al., 1999). These drugs cause damage that is directly related to GORD. NSAIDS were discussed previously under concurrent medical condition . In cases where subjects still require using the NSAIDS, NICE guidelines (GC017) recommends the u e of proton pump inhibitors (PPI) for the protection of the gastric mucosa. **COXIB inhibitor** was used in 9.5% *(n*=20) of the subjects without gastroscopy and 12.5% *(n*=47) of the subjects with gastroscopy. **COX 2 inhibitor** was used in 4.3% *(n*=9) of the subjects without gastroscopy and 3.5% *(n*=13) of the subjects with gastroscopy. Currently, the cardiovascular safety of all selective and non-selective COX II inhibitors is being questioned. Lipoxins that are in phase 2 trails are currently being investigated as a replacement for selective and non-selective COX II inhibitors (Souza et al., 2003). The COX inhibitors were discussed previously under rheumatoid arthritis.

Aspirin was used in 6.6% *(n*=14) of the subjects without gastroscopy and 5.3% *(n*=20) of the subjects with gastroscopy. The frequency of aspirin use was lower in the subset with ga troscopy. The use of the gastroscopy confirmed the diagnosis of GORD and discouraged the use of drugs that aggravate GORD. Aspirin is known for its direct damage to the gastric mucosa thus aggravating GORD. According to NICE guidelines (GC017) the drugs causing irritation to the stomach lining must be stopped. If it cannot be stopped then another medication must be co-prescribed to relieve the symptoms of dyspepsia. Clopidogrel (Plavix ®) is commonly used in subjects with aspirin–gastrointestinal tract sensitivity as shown in the CAPRIE (Clopidogrel versus Aspirin in Subjects at Risk of Ischaemic Events) trial (American College of Cardiology-American Heart Association guidelines; Lie, 2005). However, more recent studies have suggested that the use of PPIs with aspirin may be more beneficial than Clopidogrel (Chan et al, 2005).

Enteric-coated aspirin was used in 12.3% *(n*=26) of subjects without gastroscopy and 8.2% *(n*=31) of subjects with gastroscopy. According to Kelly et al., (1996), cardioprotective doses of aspirin are associated with increased risk of ulceration. Therefore an alternative drug such as clopidogrel could be used or a PPI could be added to aspirin in these subjects as mentioned previously.

Calcium Channel Blockers was used in 10% (*n*=21) of subjects without gastroscopy and 11.7% (*n*=44) of subjects with gastroscopy. The frequency of calcium channel blockers use was lower in the subset without gastroscopy. Calcium channel blockers affect the lower oesophageal sphincter tone (Kinnear et al., 1999). According to the NICE (CG017) guidelines, calcium channel blockers should be avoided if the subject is experiencing the symptoms of GORD. The clinician should try an alternate drug treatment for the relevant diagnosis.

Alendronate (Fosamax®) was used in 25 subjects, 5.2% *(n*=11) without gastroscopy and 3.7% *(n*=14) with gastroscopy. Alendronate causes oesophageal mucosal injury thus aggravating GORD (Kinnear et al., 1999). However, Risedronate (Actonel®) is associated with lesser gastro intestinal side effects than alendronate (Barclay, 2003). **Theophylline** was used in 2.4% *(n*=5) of subjects without gastroscopy and 2.9% *(n*=11) of subjects with gastroscopy. Theophylline affects the lower oesophageal sphincter tone (Kinnear et al., 1999). It also irritates the oesophageal mucosa (Nevin, 2000). **Warfarin** was used in 1.9% *(n*=4) of subjects without gastroscopy and 3.5% *(n*=13) of subjects with gastroscopy. Warfarin causes gastrointestinal mucosal injury thus aggravating GORD.

Methotrexate (DMARDS) was used in 1.4% (*n*=3) of subjects without gastroscopy and 1.1% (*n*=4) of subjects with gastroscopy. Methotrexate is documented to cause direct damage to the gastric mucosa thus aggravating GORD. **Corticosteroids** were used in 2.8% (*n*=6) of subjects without gastroscopy and 2.4% (*n*=9) of subjects with gastroscopy. Corticosteroids cause gastrointestinal mucosal injury thus aggravating GORD (Lazenby et al., 2002). These drugs should be used for short-term therapy only due to their severe side effects on the body. Ulcerogenic drugs use were lesser in subjects with gastroscopy. According to NICE (CG017) guidelines the drugs causing irritation to the stomach lining must be stopped. If the medication cannot be stopped, then a PPI needs to be added to the treatment.

4.4 Complications in relation to the number of gastroscopies

Subjects with GORD present with both oesophageal and extra-oesophageal complications. Individual oesophageal complications of GORD will be presented and evaluated.

Table 10: Analysis of complications in subjects with or without gastroscopy.

	Subjects without gastroscopy % *(n)*	Subjects with gastroscopy % (n)		
Number of gastroscopy	0	1	> 1	Total
Complications	7 (15)	21 (49)	34 (48)	25.9 (97)
Without complications	93 (196)	79 (183)	66 (95)	74.1 (278)
Total	211	232	143	375

Complications of GORD were evaluated in subjects with and without gastroscopy. Subjects with gastroscopy were further identified as those having one gastroscopy or more that 1 gastroscopy.

Analysis of subjects with complications in subjects with or without gastroscopy.

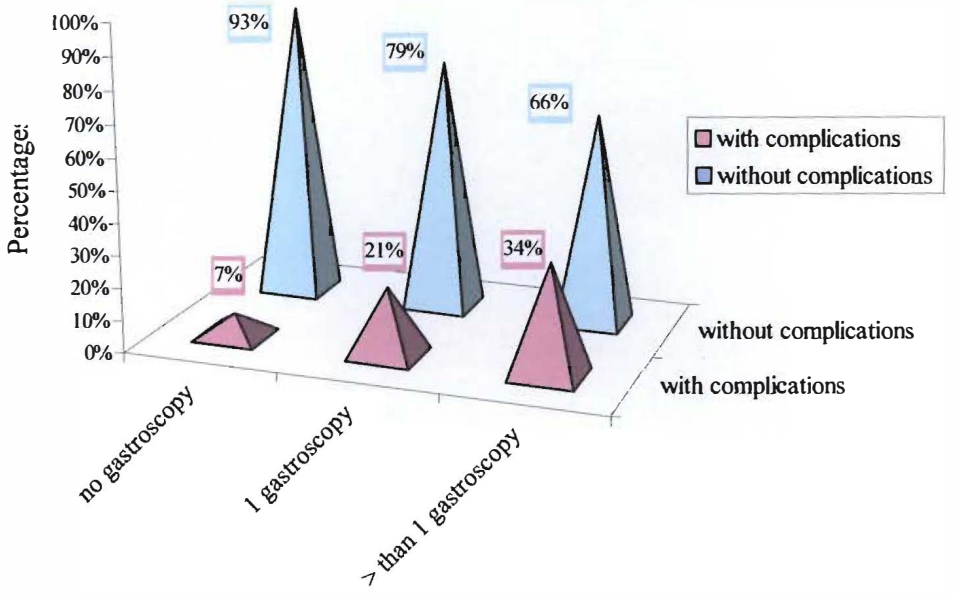

Figure 3: Analysis of subjects with complications in subjects with or without gastroscopy.

Figure 3 presents the increased number of complications detected in subjects with greater than 1 gastroscopy (34%; n=48) as compared to subjects with 1 gastroscopy (21%; n=49) or without gastroscopy (7%; n=15). In subjects where symptoms have not resolved or have complications of GORD (oesophageal or extra-oesophageal), the need for 1 or more gastroscopies exists. There was a statistically significant difference in detecting complications between the subjects with and without gastroscopy ($p<0.001$).

This result is expected, since gastroscopy is a diagnostic tool, which aids in the diagnosis of complications. According to NICE (CG017) guidelines, gastroscopy should be performed on subjects with complications and in cases not responding to standard treatment.

Subjects without gastroscopy presented with the lowest number of complications (7%; n=15). The performance of gastroscopy in these subjects may have resulted in more

complications being detected. The decision to perform a gastroscopy should be based on whether the subject had complications of GORD or if the symptoms of GORD have not resolved after empirical therapy (NICE GC017). The clinician needs to base his/her diagnosis on objective evidence (gastroscopy) and not only on symptoms. Subjects with serious complications may remain undetected.

93% (*n*=196) of subjects without complications were in the group without gastroscopy. Gastroscopy is an objective measure and the lack thereof may lead one to speculate that if gastroscopy were performed, more complications may have been detected. One or more serious complications of GORD could have remained undetected. According to NICE (CG017) guidelines, gastroscopy should be performed on subjects with complications and in whom symptoms have not resolved.

74.1% (*n*=278) of the study population with gastroscopy presented without complications. Subjects without alarming symptoms should be treated empirically for 2 months (NICEGC017), which would eliminate the need for gastroscopy and hence reduce medical expenses. One of the key discussions and conclusions in the GENVAL Guidelines (Dent et al., 1999) was that subjects with a typical history of uncomplicated GORD should be given empirical therapy after careful symptom analysis without diagnostic investigation. If this fails, or if the subject has symptoms suggesting complications, they should undergo a gastroscopy. The South African Gastroenterologists Society (SAGES) supports and endorses the GENVAL guidelines (SAGES website, 2006). If the symptoms continued or if they developed complications, then gastroscopy is indicated.

According to the NICE (CG017) guidelines, routine endoscopic investigation of subjects, presenting with dyspepsia and without alarming symptoms, is not necessary. However, for subjects over 55years of age with complications, gastroscopy should be considered. According to the NICE (CG017) guidelines, a subject presenting with dyspepsia and without alarming symptoms should be offered 1-2 months of full dose PPI. The American College of Gastroenterology (Good et al., 2003) and the British Society of Gastroenterology (BSG) also suggests the empiric treatment of PPIs in subjects without alarm symptoms.

The percentage of subjects without complications in both the groups confirms that the 2 groups in this study were not chosen due to their complications.

Subjects with gastroscopy were further subdivided into those having one and those with more than 1 gastroscopy. Subjects with complications and 1 gastroscopy were 21% *(n*=49) whereas subjects with greater than 1 gastroscopy and complications were 34% *(n*= 48). There was a statistically significant difference in detecting complications between the subjects with 1 or more than 1 gastroscopy ($p<0.001$). The proportion of subjects with complications detected is significantly associated with the number of gastroscopies they received. The odds or chances of detecting complications were significantly greater in subjects with a single gastroscopy when compared to those without gastroscopy. Having more than 1 gastroscopy increased the odds of detecting complications significantly compared to subjects with just one gastroscopy, (OR 1.9; 95% CI: 1.1 – 3.1). This is in accordance with international guidelines, which recommend more than 1 gastroscopy in non-resolving complications of GORD.

Treatment of GORD associated with Barrett's oesophagus has not been shown to eliminate the metaplasia of that condition or the risk of malignancy. Consequently, subjects with Barrett's oesophagus require a periodic endoscopic biopsy to assess oesophageal tissue for malignant changes (Kahrilas, 1996). Subjects with strictures on an initial endoscopic examination will need follow-up to evaluate for underlying Barrett's oesophagus that may have been missed on the initial examination because the presence of mucosal erosions/ulcerations may have obscured the identification of underlying Barrett's disease (Fennerty, 2003).

Gastroscopy is useful for diagnosing the complications of GORD, such as Barrett's oesophagus, oesophagitis and strictures, but it is not sensitive for diagnosis of GORD itself. Only 50 percent of subjects with GORD manifest macroscopic evidence on endoscopy. Some subjects with GORD are not positively identified even after having a gastroscopy performed (Schenk et al., 1997).

Table 11: Complications directly related to GORD in subjects with or without gastroscopy

Complications	No gastroscopy % (*n*)	1 gastroscopy % (*n*)	>1 gastroscopy % (*n*)	Total (≥1 gastroscopy) % (*n*)	p value
Ulcerative oesophagitis	0.5 (1)	3 (7)	2.7 (4)	3 (11)	0.06
Oesophageal erosions	0.5 (1)	1 (3)	2.7 (4)	1.9 (7)	0.3
Oesophageal stricture	3 (6)	2.4 (6)	4.8 (7)	3.4 (13)	0.8
Barretts oesophagus	2 (4)	12 (28)	21.7 (31)	15.7 (59)	<0.001
Cough	0 (0)	0.4 (1)	0(0)	0.3 (1)	0.9
Chest pain	0 (0)	2 (4)	0(0)	1.2 (4)	0.3
Nocternal dyspnea	0.5 (1)	0(0)	0(0)	0	0.4
Reflux laryngitis	0.5 (1)	0(0)	0.7 (1)	0.3 (1)	0.9
Reflux into mouth	0 (0)	0(0)	0.7 (1)	0.3 (1)	0.9

Table 11 lists the 10 most common complications found in the study population. There was a statistically significant increase in the detection of Barretts oesophagus in the subset with gastroscopy as compared with the subset without gastroscopy ($p<0.001$).

4.5 Complications of GORD

4.5.1 Oesophageal complications of GORD

Possible complications include oesophageal erosions, ulcer, stricture and Barrett's oesophagus or adenocarcinoma. Barrett's oesophagus and adenocarcinoma are the most serious complication of GORD (Kahrilas, 2003).

Oesophageal complications of GORD in patients with and without gastroscopy done

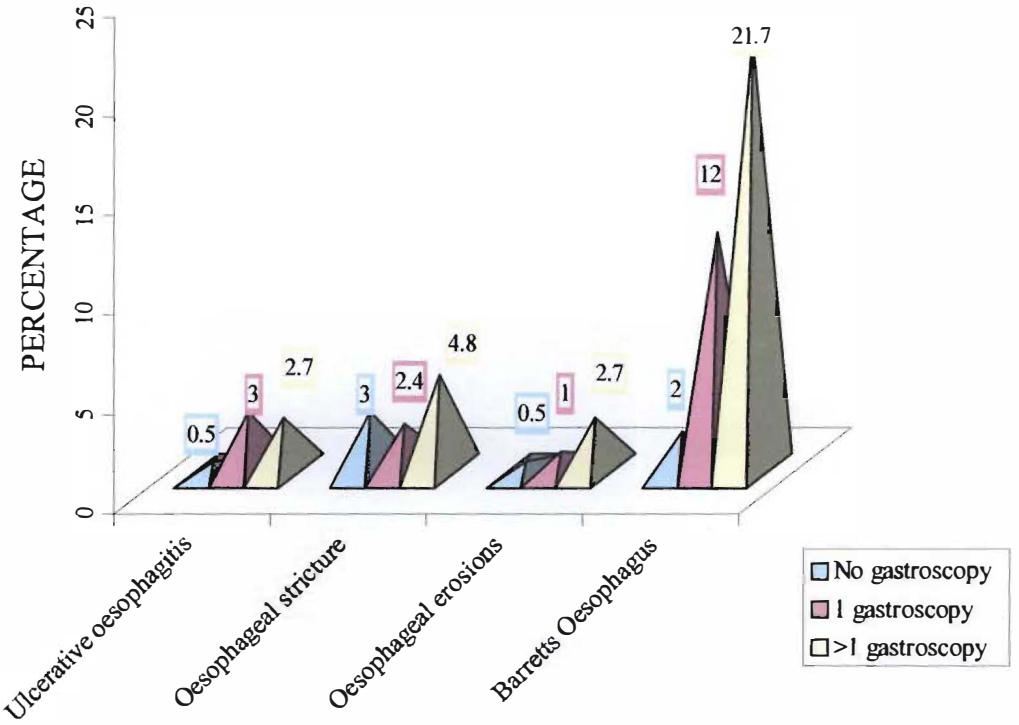

Figure 4: Oesophageal complications directly related to GORD in subjects with or without gastroscopy

The choice of the 2 subsets was based on whether they had a gastroscopy performed or not. The diagnosis of GORD was based on the Los Angeles Classification or Savary-Miller classification for GORD (appendix 7). Very few incidences of ulcerative oesophagitis, oesophageal stricture and oesophageal erosions were found in subjects without gastroscopy (4%, n=8) and with gastroscopy comprised (8.3%, n=31). This study did not have subjects with adenocarcinoma.

With respect to Barretts oesophagus, subjects without gastroscopy comprised of 2% (n=4) whereas those with gastroscopy comprised 15.7% (n=59) (Table 11). This difference was statistically significant ($p<0.001$). Barrett's oesophagus occurs in a small percentage of subjects with chronic diseases. It is a serious form of GORD, which may eventually develop

due to erosion, which can lead to cancerous changes in the tissue lining of the oesophagus. This is a very serious consequence of GORD and requires appropriate treatment. Subjects with complications of GORD need to use an objective criteria (gastroscopy) to detect complications and treat appropriately and timeously. The current practice of most physicians is to perform endoscopic surveillance every 2 to 3 years in subjects with Barrett's oesophagus, with increased frequency if dysplasia is detected (Falk, 2000).

4.5.1.1 Ulcerative Oesophagitis

In subjects with gastroscopy, ulcerative oesophagitis was found in 3% *(n*=11) of the subjects whereas in subjects without gastroscopy, ulcerative oesophagitis was found in 0.5% *(n*=1) of subjects [not statistically significant different (p=0.06)]. This was possibly due to the low incidence of ulcerative oesophagitis in this study population. Ulcerations are excavated defects in the oesophageal mucosa that result when epithelial cells succumb to the caustic effects of refluxed acid and pepsin (Spechler, 2003).

According to Kahrilas (1993), ulcerative oesophagitis is an uncommon complication of gastro-oesophageal reflux disease, occurring in only 5% of subjects with reflux oesophagitis. In a study by Reynolds (1996), ulcerative oesophagitis occurred in 3.5% of the population. Good et al., 2003 in the National Guideline Clearinghouse guidelines showed ulcerative oesophagitis occurring in 2%-7% of the subjects. The results of the present study population of subjects with gastroscopy was within the range of studies mentioned above.

The results of this study compared favourably with international studies. However, in subjects without gastroscopy, the number of subjects with ulcerative oesophagitis was low 0.5% *(n*=1). If gastroscopy was performed, more complications may have been detected and more aggressive treatment may have ensured quicker healing time. These subjects are more likely to develop complications and become more resistant to treatment (Reynolds, 1996). Subjects with ulcerative oesophagitis should be diagnosed objectively with a gastroscopy. This indicates the need to treat subjects with complications appropriately and immediately. This also necessitates the use of a gastroscopy in subjects with complications.

4.5.1.2 Oesophageal Stricture

In subjects with gastroscopy, oesophageal stricture was found in 3.4% (*n*=13) of subjects whereas in the subjects without gastroscopy, oesophageal stricture was found to be 3% (*n*=6). In subjects with and without gastroscopy, the percentage of subjects in whom oesophageal strictures occurred was similar. A gastroscopy may not be necessary for the diagnosis of oesophageal stricture. Diagnosis could be based on presence of dysphagia. These subjects also present with the following symptoms namely odynophagia (pain on swallowing) and food impaction (Nevin, 2000).

Oesophageal ulcers can stimulate fibrous tissue production and collagen deposition resulting in stricture formation (Spechler, 2003). This complication occurs in 4% to 20% of subjects with reflux oesophagitis (Kahrilas and Hogan, 1993). Good et al., 2003 also showed that this complication occurred in 4% to 20% of subjects. The results of the present study population fell into the lower end of the prevalence studies when compared to international studies.

Anti-reflux therapy has been shown to reduce the need for recurrent dilation from oesophageal stricture formation (National Guideline Clearinghouse, 2002). Subjects with strictures on an initial endoscopic examination will need follow-up to evaluate the presence of underlying Barrett's oesophagus that may have been missed on the initial examination. This can occur when the presence of mucosal erosions/ulcerations obscures the identification of underlying Barrett's disease (Fennerty, 2003).

4.5.1.3 Oesophageal Erosions

In subjects with gastroscopy, erosive oesophagitis was found in 1.9% (*n*=7) of subjects whereas as in subjects without gastroscopy, erosive oesophagitis was found to be in 0.5% (*n*=1) of subjects. There was no statistically significant difference between the subjects with and without gastroscopy.

Peptic oesophageal erosions are excavated defects in the oesophageal mucosa that result when epithelial cells succumb to the caustic effects of refluxed acid and pepsin. Uncommonly, oesophageal ulcers are complicated by hemorrhage, perforation, and penetration into the airway (Spechler, 2003). These subjects present with the following

symptoms: haemorrhage, fatigue and/or anaemia (Nevin, 2000) and require iron replacement therapy. In subjects with GORD, 20% to 40% of subjects present with erosive oesophagitis (Cash, 2003). In our study, there were a lower number of subjects with erosive oesophagitis as compared to the study by Cash (2003). One subject without gastroscopy presented with erosive oesophagitis. It is possible that if more gastroscopies were undertaken in these subjects, more of these complications may have been detected.

Subjects with erosive oesophagitis are at risk of complications of oesophagitis, including bleeding, stricture and Barrett's oesophagus (Schneider, 2002). It is important to treat erosive oesophagitis timeously since this condition leads to more serious complications. Subjects with erosive oesophagitis on an initial endoscopic examination will need follow-up to evaluate for underlying Barrett's oesophagus. This may be missed on the initial examination because the presence of mucosal erosions/ulcerations can obscure the identification of underlying Barrett's disease (Fennerty, 2003). This was also the case with oesophageal strictures as mentioned previously. All male subjects with GORD should be routinely investigated for unexplained anaemia in order to rule out erosive oesophagitis.

4.5.1.4 Barretts oesophagus

Table 12: Frequency of Barretts oesophagus in subjects with or without gastroscopy

Variable		Subjects without gastroscopy % (*n*)	Subject with gastroscopy % (*n*)
Sex	Male	0.5 (1)	10.9 (41)
	Female	1.4 (3)	4.8 (18)
Age	>55 years	1 (2)	9.9 (37)
	<55 years	1 (2)	5.9 (22)
Ethnicity	African	0(0)	0(0)
	Coloured	0(0)	0(0)
	Indian	0(0)	1.3 (5)
	White	1.9 (4)	14.4 (54)
Barretts oesophagus	Yes	1.9 (4)	15.7 (59)
	No	98 (207)	84.3 (316)

Barretts oesophagus was found in 15.7% (n=59) of subjects with gastroscopy and 1.9% (n=4) of subjects without gastroscopy. This difference was statistically significant ($p<0.001$). Barrett's oesophagus is reported in approximately 12% of subjects with symptomatic reflux (Kinnear, 1999). Navaratnam (1998) found Barretts oesophagus to occur in approximately 13% of the GORD population. The international studies compare favourably to the subset with gastroscopy in this study.

In subjects without gastroscopy, the prevalence of Barretts oesophagus was low. The proportion of subjects with complications is strongly associated with the number of gastroscopies they underwent. Multiple gastroscopies increased the likelihood of detecting complications.

In Barretts oesophagus, the normal stratified squamous epithelium of the distal oesophagus is replaced with metaplastic, columnar epithelium resembling that of the intestinal mucosa. This replacement is an attempt by the body to protect the oesophagus from further injury. Barretts tissue can undergo dysplastic changes and may lead to oesophageal adenocarcinoma.

Treatment of GORD associated with Barrett's oesophagus has not been shown to eliminate the metaplasia of that condition or the risk of malignancy. Consequently, subjects with Barrett's oesophagus require periodic endoscopic biopsy to assess oesophageal tissue for malignant changes (Fennerty et al., 1996). This indicates the necessity of using an objective criteria (gastroscopy) in detecting complications. This would result in complications being detected timeously. These subjects often remain asymptomatic until the development of an associated complication (strictures, adenocarcinoma) (Nevin, 2000). This further emphasises the need for gastroscopies in subjects with complications.

The subset with gastroscopy had a higher percentage of white male subjects with Barrett's oesophagus. International studies have shown that Barrett's oesophagus occurs more often in white males (Gopal, 2001). Endoscopy to screen for Barrett's oesophagus is recommended in subjects with a long duration of GORD symptoms (e.g. > 5 years), in particular white males who are 50 or more years of age (Good et al., 2003). It would seem that GORD occurs more in the economically advantaged communities and in urban areas. Complicated gastro-oesophageal reflux disease appears to be predominantly a disorder of whites (Spechler, 2002).

Gastroscopy is a diagnostic tool and the lack of its use in some subjects may account for the small number of Barrett's oesophagus detected in subjects without gastroscopy (n=4). Subjects with complications of GORD should undergo endoscopic evaluation. Gastroscopy is essential to detect Barrett's oesophagus, thus endoscopic surveillance every 2 to 3 years may be inappropriate since Barrett's oesophagus has to be treated quickly and as early as possible. If dysplasia is detected, gastroscopy needs to be performed on a yearly basis.

4.5.2 Extra-oesophageal complications

Extra-oesophageal complications occur in subjects with GORD, however these complications did not form part of the results. These complications include atypical symptoms of chronic chest pain, cough, hoarseness, asthma and dental erosions. These subjects may or may not have typical symptoms of GORD and are often best diagnosed with an empirical trial of therapy. It has been suggested that these subjects may require higher doses of acid suppression therapy and longer duration of therapy than subjects with more typical oesophageal symptoms of GORD (DeVault et al., 1999).

4.6 Duration of treatment

The majority of subjects were treated with PPIs (See table 16).

Table 13: Duration of GORD treatment in subjects with or without gastroscopy

Number of months	Subjects without gastroscopy % *(n)*	Subjects with gastroscopy % *(n)*
Less than 6 months	9.5 (20)	32 (120)
6-12 months	14.2 (30)	30 (113)
≥ 12 months	76.3 (161)	38 (142)

More subjects (76.3%) without gastroscopy were treated for greater than 12 months. This was statistically significant ($p<0.001$).

9.5% *(n*=20) of subjects without gastroscopy were treated for less than 6 months and 32% *(n*=120) of subjects with gastroscopy were treated for less than 6 months, for GORD. According to international guidelines, subjects without alarming symptoms should be treated for 2 months. According to Table 10, 93% *(n*=196) of subjects in the subset without gastroscopy did not have complications and in the subset with gastroscopy, 74.1% *(n*=278) did not have complications. Since a large number of subjects with gastroscopy did not have complications, these subjects could have been treated empirically. It may be concluded that clinicians did not follow the guidelines when treating subjects without alarming symptoms in both the subsets that were treated for less than 6 months. If subjects were treated according to the international guidelines, a higher percentage of subjects may have been treated for less than 6 months. 32% (*n*=120) of subjects with gastroscopy who were treated for less than 6 months may not have needed a gastroscopy performed. In these subjects symptoms may have resolved after empirical therapy. The cost of the gastroscopy and other associated medical costs may have been avoided.

76.3% *(n*=161) of subjects without gastroscopy were treated for >12 months and 38%*(n*=142) of subjects with gastroscopy were treated for >12 months. According to Table

10, 7% (n=15) of subjects in the subset without gastroscopy had complications and in the subset with gastroscopy, 25.9% (n=97) had complications. Although subjects had a lower percentage of complications in these groups, they were treated for a longer duration of time. Subjects with complications need to be treated for a longer period of time. This is due to the mucosal damage that has occurred over a period of time, which has lead to serious complications (Barrets oesophagus, oesophageal strictures). According to NICE (GC017) guidelines, subjects who have severe GORD symptoms or who have a proven pathology (e.g. oesophageal ulceration, Barrett's oesophagus) should be treated with a higher healing dose of a PPI (refer to appendix 1) until symptoms have been controlled. Subjects without gastroscopy need to be objectively assessed in order to determine whether they have complications to warrant a longer duration of treatment of PPIs.

Based on the results obtained, one could recommend that subjects with uncomplicated GORD be treated with 2 months empirical therapy of PPI. Only if symptoms do not resolve or if these subjects have complications or alarming symptoms, then only should a gastroscopy be performed. However, the only exception to this would be subjects >55years who present with symptoms of GORD for the first time. They should have a gastroscopy performed (NICE GC017).

4.7 The Cost of GORD Treatment

The cost of the drugs was based on the pricing system used by the medical aid (Pharmaceutical Computer Data) for the time period January 2002 to December 2003. The drugs used for the treatment of GORD were mostly proton pump inhibitors, motility stimulants and H_2 receptor antagonist (table 16).

Table 14: Cost of treatment in subject within 2 year period

	Without gastroscopy (*n*=211)		With gastroscopy (*n*=375)	
	Total cost	Cost per subject	Total cost	Cost per subject
Cost of drugs	R448 939(211)	R2127	R2 876 990 (375)	R7672
Cost of gastroscopy	----	----	R126769 (375)	R338
Total cost	R448 939(211)	R2127	R3003759 (375)	R8010

The approximate cost of gastroscopy per subject is R338 per 2-year period. The approximate cost of drugs per subject with gastroscopy is R7672 (table 14). This gives a total cost of treatment per subject with gastroscopy of approximately R8010. This cost includes the cost of drugs and gastroscopy and excludes theatre fees, gastroenterologist consultation, ward fees and theatre drugs. The cost of treatment per subject without gastroscopy is approximately R2127. The cost of treatment per subject for subjects with gastroscopy (R8010) is 3.8 times more than subjects without gastroscopy (R2127). However, gastroscopy is an objective criteria, which leads to the detection of complications and hence more intense and directed treatment.

It would seem less expensive to treat those subjects without gastroscopy. However, based on pharmacoeconomic principles, it costs more in the long term to treat subjects who did not have a gastroscopy performed. Undetected and therefore untreated complications result in resistance to treatment, prolonged healing time, which may lead to Barrets oesophagus and adenocarcinoma. This results in costs escalating. There is a need for gastroscopy in subjects with complications and in whom symptoms have not resolved.

Of subjects with gastroscopy, 74.1% (*n*=278) (table 10) did not have complications. A precondition for gastroscopy is the presence of complications and many of these subjects may have been unnecessarily exposed to a gastroscopy. As mentioned previously, it is recommended that these subjects should be treated empirically for approximately 2 months before having a gastroscopy. If the symptoms persist or if there are complications or alarming symptoms of GORD (CG017 NICE guideline), then only should a gastroscopy performed. There would have been a cost saving in direct (gastroscopy) and indirect (theatre fees, gastroenterologist consultation, ward fees, theatre drugs) medical expenses.

Table 15: Cost of drugs to treat oesophageal complications in the study population within 2 year period

Complication	Subjects without gastroscopy R *(n=12)*		Subjects with gastroscopy R *(n=90)*	
	Total cost	Cost per subject	Total cost	Cost per subject
Ulcerative oesophagitis	1912 (1)	1912	97633 (11)	8876
Barretts oesophagus	16316 (4)	4097	370,064.00 (59)	6272
Oesophageal stricture	25141 (6)	4190	64875 (13)	4990
Oesophageal erosions	3076 (1)	3076	22002 (7)	3143
Total	46445	3870	554,574.00	6160

The total cost of medication per subject with complications of GORD (table 15) with gastroscopy (R6160) is more than for subjects without gastroscopy (R3870). While the cost per subjects for the subset with gastroscopy was higher, the diagnosis of GORD was conclusive. Therefore, it allows for targeted therapy based on conclusive evidence.

Ulcerative oesophagitis, Barretts oesophagus, oesophageal stricture, oesophageal erosions cost R8876, R6272, R4990, R3143 respectively per subject for subjects with gastroscopy compared to R1912, R4097, R4190, R3076 for those without gastroscopy. Although the expense incurred in the subset with gastroscopy is higher, in the long term it is more cost effective since the complications will be detected and treated timeously and effectively. According to NICE (GC017) guidelines, subjects who have severe gastro-oesophageal reflux disorder (GORD) symptoms or who have a proven pathology (e.g. oesophageal ulceration, Barrett's oesophagus) should be treated with a higher (refer to appendix 1) healing dose of a PPI until symptoms have been controlled.

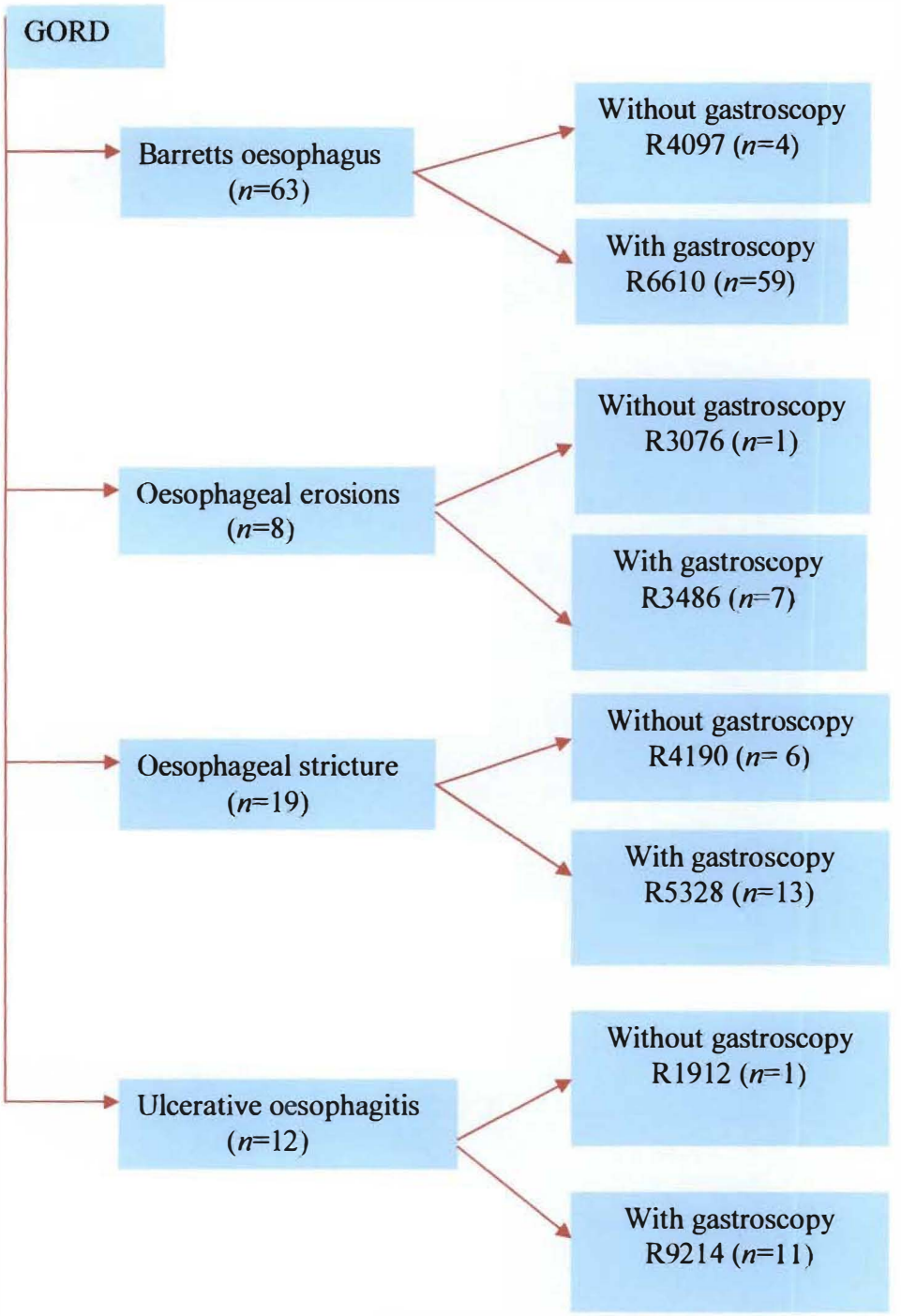

Figure 5: Schematic representation of cost of drugs and gastroscopy per subject (January 2002-December 2003)

The cost in the above schematic representation includes the cost of drugs and gastroscopy (R338) per subject. For example, in subjects with Barretts oesophagus, the cost of the drugs was R6272 and cost of gastroscopy was R338. In combination, the total cost for both gastroscopy and drugs was R6610.

4.8 Classes of drugs

Table 16: Classes of drugs used for GORD

Drugs used for GORD	Subjects without gastroscopy % (*n*)	Subjects with gastroscopy % (*n*)
Proton Pump Inhibitors	84 (178)	87.6 (331)
Motility Stimulants	6.1 (13)	6.3 (24)
H2 Receptor Antagonist	5.7 (12)	2.9 (11)
Others	2.4 (5)	1.6 (6)
Anti-regurgitants	0.9 (2)	0.8 (3)
Mucosal protective agents	0.9 (2)	0.8 (3)
Total subjects	211	375

Proton Pump Inhibitors (PPI) were used in 84% (*n*=178) of subjects without gastroscopy and 87.6% (*n*=331) with gastroscopy. This concurs with international and national guidelines, which advocates the use of PPIs as first line agents in GORD. Proton-pump inhibitors (PPIs) form the cornerstone of treatment for GORD and have been documented to be superior to H_2-receptor antagonists (H_2RA) in meta-analyses for the healing of erosive oesophagitis (Sharma, 2003). The Genval Workshop Guideline recommends PPI therapy as the initial medical treatment of choice because of the clearly superior efficacy resulting in the most prompt achievement of desirable outcomes at the lowest overall cost (Zuber, 1999). The NICE guidelines also advocate the use of PPIs as first line treatment for GORD.

As mentioned previously, according to NICE guidelines, subjects who have severe gastro-oesophageal reflux disorder (GORD) symptoms or who have a proven pathology (e.g. oesophageal ulceration, Barrett's oesophagus) should be treated with a higher healing dose of a PPI (refer to appendix 1) until symptoms have been controlled. Once healing has been achieved, the dose should be stepped down to the lowest dose that maintains control of symptoms. Regular low dose (refer to appendix 1) maintenance of most PPIs will prevent recurrent GORD symptoms in 70-80% of subjects and should be used in preference to the higher healing dose (NICE GC017). Where necessary, should symptoms re-appear, the

higher dose should be recommenced. In complicated oesophagitis (stricture, ulcer, haemorrhage), the high dose should be maintained.

PPI therapy has been shown to be more effective than H_2 receptor antagonist (H_2RA) therapy for maintenance of GORD healing. Metz and colleagues (2003) reported the results of 2 large studies evaluating the effectiveness of pantoprazole (PPI) compared with ranitidine (H_2RA) for preventing recurrence of severe GORD. They found that subjects treated with ranitidine were more likely to experience recurrence of severe GORD compared with subjects treated with pantoprazole. This study confirms the superiority of PPIs over H_2RA.

Table 17: Proton pump inhibitors used in study

	Subjects without gastroscopy % (*n*)	Subjects with gastroscopy % (*n*)
Lansoprazole (Lanzor®)	28(69)	36(119)
Omeprazole (Losec®, Ulzec®)	27(64)	22(71)
Pantoprazole (Controloc®, Pantoloc®)	22(53)	22 (71)
Esomeprazole (Nexiam®)	11(26)	13(42)
Rabeprazole (Pariet®)	12(28)	8(28)

Omeprazole was the first PPI introduced in clinical practice in South Africa, followed by lansoprazole, rabeprazole, pantoprazole and finally esomeprazole. According to this study, the PPI most commonly used was lansoprazole in subjects with and without gastroscopy and omeprazole was the second most commonly prescribed PPI. This may be due to omeprazole and lansoprazole being the longest in the market or due to the lower costing generic products available.

All PPIs block the proton pump and thus acid secretion from parietal cells. This results in more complete acid suppression (Annis, 2003). The different PPIs have unique pharmacokinetic properties and pharmacodynamic activity but do not necessarily indicate differences in clinical efficacy. No head to head studies have yet been done to compare whether clinical difference does occur between the different PPIs (Vakil and Fennerty, 2003). Differences were found between the standard doses of proton pump inhibitors with regard to the onset of symptom relief in gastro-oesophageal reflux disease (lansoprazole was faster

than omeprazole, and esomeprazole was faster than both lansoprazole and omeprazole) and the healing of oesophagitis (esomeprazole was superior to both omeprazole and lansoprazole). Despite these differences, there is as yet insufficient data to establish the superiority of any one agent over all others across all disease states treated with these agents (Vakil and Fennerty, 2003).

The proton pump inhibitors are highly protein bound (95-98%) and have short plasma half-lives ranging from 0.5 to 2 hours. The proton pump inhibitors are extensively metabolized by the CYP450 isoenzyme system. With the exception of omeprazole, the proton pump inhibitors are classified as Pregnancy Category B (appendix 8). Omeprazole is classified as Pregnancy Category C (appendix 8). There are, however, no well-controlled studies in pregnant women and these drugs should be used only if clearly needed. Esomeprazole differs from other proton pump inhibitors in that it is the first proton pump inhibitor developed as a single optical isomer. It consists of only the S-isomer of omeprazole (Annis, 2003).

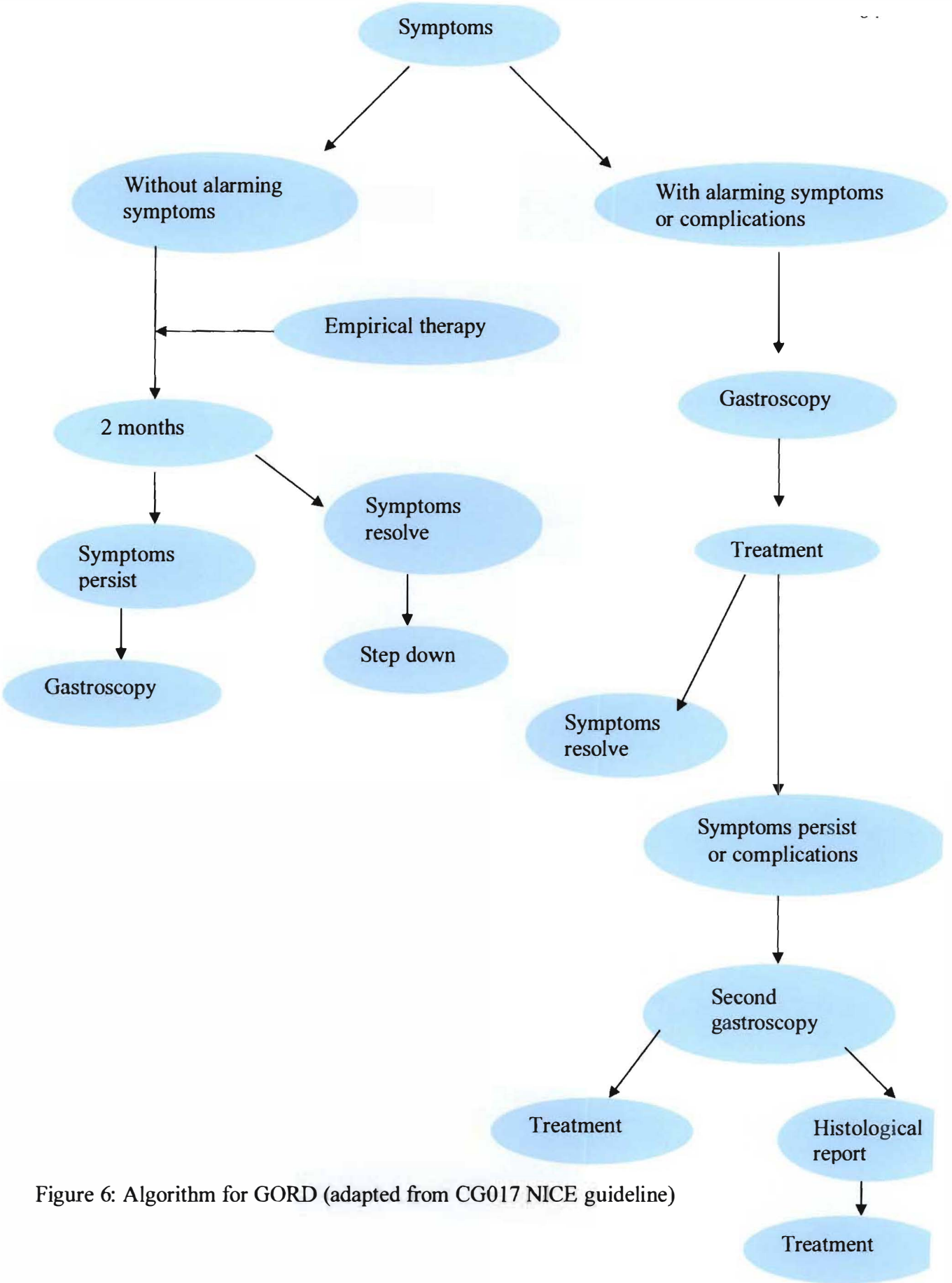

Figure 6: Algorithm for GORD (adapted from CG017 NICE guideline)

4.9 Summary of findings

The 2 subsets of subjects identified in this study were those with and without gastroscopy. The highest prevalence of GORD was found amongst white South Africans. Proton Pump Inhibitors (PPI) therapy was used as the medical treatment of choice because of the clearly superior efficacy over H_2RA. Drugs used for concurrent diagnosis that aggravates GORD need to be discontinued and an alternative treatment should be considered. If these drugs cannot be discontinued, a proton pump inhibitor should be added to the subject's drug treatment.

The highest number of **complications** was detected in subjects **with gastroscopy**. Gastroscopy is necessary in subjects with complications and in whom symptoms have not resolved. Subjects with oesophageal complications of GORD need to be diagnosed objectively with a gastroscopy. Certain subjects with oesophageal complication may require more than 1 gastroscopy to monitor serious complications. The highest prevalence of Barretts oesophagus was detected in subjects with gastroscopy, especially in the white male population. A large number of subjects **without complications** were observed in the subset **with gastroscopy**.

According to the NICE guidelines, these subjects should have first been treated empirically before having a gastroscopy performed. In the subset with gastroscopy, 74.1% (278) of subjects did not have complications. In these subjects, cost per subject would have been lower if these subjects were treated empirically before having a gastroscopy performed. The cost per subject for the time frame of the study was approximately R8010 per subject, which included the cost of drugs and gastroscopy. In order to save costs, subjects should be treated empirically for 1-2 months and if symptoms do not resolve, or if there are complications or alarming symptoms, then only should a gastroscopy be performed in order to detect complications.

As expected, the lowest number of **complications** was detected in subjects **without gastroscopy**. Gastroscopy is a necessary objective criterion to be used to detect complications. Subjects with strictures may not need to be diagnosed using the gastroscopy since dysphagia is the identifying symptom. The highest number of subjects **without complications** was observed in the subset **without gastroscopy.** These subjects should have

first been treated empirically before having a gastroscopy performed. The cost per subject for the time frame of the study was approximately R2127 per subject, which included the cost of drugs. According to the study, it costs less to treat subjects without gastroscopy. While it would appear less expensive to treat subjects without gastroscopy, using pharmacoeconomic principles, it costs more in the long term to treat subjects who did not have a gastroscopy performed. This would be due to undetected, untreated and therefore treating resistant complications.

CHAPTER FIVE: LIMITATIONS, RECOMMENDATIONS AND CONCLUSION

5.1 Limitations

The study population was restricted to people who could afford medical aid which may be a source of selection bias.

This study was confined to a single medical aid society. For comparison, data from other medical aid societies should be included.

As with all retrospective studies, available subject data was limited to that provided by the practising physician to the Medical Aid Society.

Many diagnoses reflected in the Medical Aid Society records are clinically made which may not be medically accurate eg erosive oesophagitis or barretts oesophagitis are diagnosis, which cannot be made clinically. These diagnoses can only be made after a gastroscopy and further investigation in the case of barretts oesophagitis where a histology specimen is required.

Due to the retrospective nature of the study, there was a lack of patient information regarding the patient's preference to the approach that the attending clinician adopts. Patient reassurance plays a significant role in therapeutic outcome. The patients should be allowed to choose whether he/she would like to be treated empirically or accurately diagnosed with a gastroscopy.

The progress of GORD after tests and treatment was not monitored objectively.

5.2 Recommendations

5.2.1 Recommendation for doctors, medical aid and management of GORD

Subjects without alarming symptoms should be treated empirically for 1-2 months, however if symptoms do not resolve or if subjects have complications, then only should a gastroscopy be performed.

Subjects presenting with alarming symptoms (dysphagia, weight loss, bleeding, abdominal mass) should be referred for gastroscopy.

Empiric trial of acid suppression may be helpful in the evaluation of those with atypical manifestations of GORD, specifically, non-cardiac chest pain.

Subjects greater than 55 years of age with unexplained and/or persistant dyspepsia alone should be referred for gastroscopy to exclude the possibility of Barretts oesophagus.

Concurrent diagnoses and therapy which may complicate the management of GORD, require appropriate management e.g. GORD and rheumatoid arthritis.
PPIs should be prescribed for subjects with concurrent diagnosis and drug treatment that aggravate GORD.

The presence of co-existing symptoms for example asthma and GORD requires differential diagnosis and the corresponding appropriate management.

Diagnoses like hiatus hernia, peptic ulcer that contribute to GORD need to be managed appropriately.

Subjects who have symptoms of GORD should be screened to eliminate cancer.

Subjects with GORD should avoid using medication that aggravate GORD for example NSAIDS, warfarin, DMARDS and calcium channel blockers.

Subjects with complications may need follow up gastroscopy. Depending on the severity of the complications for example Barretts oesophagus, subjects may need to be monitored on a yearly basis.

Gastroscopy should not be performed in subjects with strictures presenting with dysphagia as a symptom.

Guidelines should be enforced. Subjects without alarming symptoms do not need a gastroscopy performed. Subjects with alarming symptoms, who have complications or in whom symptoms have not resolved, need to have a gastroscopy performed.

5.2.2 Recommendation for Patient education

Subjects need to modify their lifestyle for example to refrain from smoking, alcohol and spicy foods and refrain from eating 2 hours before sleeping.

Drugs aggravating GORD should be avoided.

Subjects need to take their medication regularly and as prescribed (after meals or before meals).

5.2.3 Recommendation for management of GORD

Futher large multicentre studies on GORD need to be conducted nationally, in the South African population, in both the private and public sectors to give a better reflection of the demographics of the disease.

To contextulise this locally or nationally, no recent studies have been performed. More studies need to be done on the South African population using data from other medical aid societies. There is currently a study being conducted by Medical Research Council on a group of subjects in Transkei who have the highest incidence of oesophageal cancer in the world.

5.3 Conclusion

In this retrospective analysis of subjects diagnosed with gastro-oesophageal reflux disease (GORD) at a private medical aid, the following was found.

- Subjects in the subset with gastroscopy had more complications of GORD as compared to the subset without gastroscopy.
- Subjects with complications of GORD or in whom symptoms have not resolved require objective criteria (gastroscopy) to diagnose GORD. These complications

included oesophageal erosions, oesophageal ulcer, oesophageal stricture and Barrett's oesophagus.

- The subjects with gastroscopy that did not have complications, should have been treated empirically first instead of having a gastroscopy performed. Gastroscopy should not be used unnecessarily unless there are complications or if symptoms do not resolve.
- Subjects without gastroscopy were treated for a longer duration as compared with subjects with gastroscopy. In these subjects the guidelines were not followed. Subjects without complications should be treated empirically for 1-2 months. The cost of treatment seemed lower for subjects without gastroscopy. However based on pharmacoeconomic principles; it costs more in the long term to treat subjects that did not have a gastroscopy performed. This would be due to undetected, untreated and therefore resistant complications.
- Drugs like NSAIDS, alendronate, calcium channel blockers and theophylline aggravate GORD. These drugs should be discontinued and if they cannot be discontinued, the use of Proton pump inhibitors (PPI) for the protection of the gastric mucosa is recommended.

It is recommended by NICE guidelines that routine endoscopic investigation of subjects of any age, presenting with dyspepsia and without alarm signs, is not necessary. These subjects should be treated empirically for approximately 1-2 months before having a gastroscopy. If the symptoms persist or if there are complications of GORD then only should a gastroscopy be performed. Gastroscopy is an objective criterion, which detects complications in subjects with GORD. Gastroscopy is not indicated if there are no complications.

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APPENDICES

Appendix 1: Proton Pump Inhibitors

Name of Drug	Low/Maintenance dose	High dose
Rabeprazole		
10 mg	x	
20 mg		x
Pantoprazole		
20 mg	x	
40 mg		x
Lansoprazole		
15 mg	x	
30 mg		x
Omeprazole		
10mg	x	
20mg	x	
40mg		x
Esomeprazole		
20mg	x	
40mg		x

Appendix 2: Concurrent Diagnosis

Concurrent Diagnosis	Subjects without gastroscopy n	Subjects with gastroscopy n	Total n
Hypertension	67	164	231
Hyperlipidaemia	53	93	146
Menopausal	52	89	141
Depressive episode	37	65	102
Osteoporosis	23	39	62
Osteoarthritis	19	36	55
Asthma	20	30	50
Ischaemic heart disease	23	26	49
Diabetes	21	27	48
Hypothyroidism	19	24	43
Rheumatoid arthritis	14	26	40
Congestive heart failure	12	17	29
Allergic rhinitis	10	13	23
Gout	10	13	23
Insomnia	9	11	20
Diaphragmatic hernia	3	16	19
Anxiety disorder,	7	10	17
Atrial fibrillation and flutter	5	12	17
Angina pectoris	8	7	15
Emphysema	4	11	15
Glaucoma	3	9	12
Irritable bowel syndrome	7	3	10
Iron deficiency anaemia	1	7	8
Soft tissue disorder	1	7	8
Anaemia	2	5	7
Epilepsy	3	4	7
Hyperplasia of prostate	2	5	7
Constipation	2	4	6

Concurrent Diagnosis	Subjects without gastroscopy n	Subjects with gastroscopy n	Total n
Neoplasm (prostrate and breast)	2	4	6
Pain	4	1	5
Parkinson's disease	2	3	5
Peripheral vascular disease	1	4	5
Diverticular disease of intestine	2	2	4
Mental disorder	1	3	4
Peptic ulcer	2	2	4
Psoriasis	2	2	4
Urinary incontinence	2	2	4
Disease of digestive system	1	2	3
Endocrine disorder	2	1	3
Myalgia	1	2	3
Oedema	1	2	3
Atopic dermatitis	1	1	2
Duodenal ulcer	1	1	2

Appendix 3: Concurrent drug therapy

Concurrent drug therapy	Subjects without gastroscopy n	Subjects with gastroscopy n	Total n
Antihypentensives	111	268	379
Lipid lowering agents	74	118	192
Inhaled corticosteriods	25	42	67
Calcium channel blockers	21	44	65
Premarin®	24	35	59
Ecotrin®	26	31	57
Eltroxin®	21	23	44
Celebrex®	8	27	35
Vioxx®	12	20	32
Disprin®	12	19	31
Nasal inhaled corticosteriods	10	18	28
Cipramil®	10	16	26
Fosamax®	11	14	25
Aropax® 20	9	13	22
Insulin	2	19	21
Trepiline®	6	14	20
Lasix®	6	13	19
Estrofem® 28	3	14	17
Mobic®	6	11	17
Warfarin®	4	13	17
Sandoz metformin®	8	8	16
Glucophage®	6	8	14
Lilly-fluoxetine®	4	9	13
Plenish k®	4	9	13
Lanoxin®	6	6	12

Concurrent Diagnosis	Subjects without gastroscopy n	Subjects with gastroscopy n	Total n
Plasmoquine®	1	11	12
Duovent® 15ml	3	8	11
Remeron®	5	6	11
Stilnox®	4	7	11
Amaryl®	5	5	10
Folic acid	5	5	10
Livifem®	4	6	10
Miacalcic® nasal	1	9	10
Activelle® fc	4	5	9
Arthrotec®	1	8	9
B-cal-d®	3	6	9
Evorel® 100	0	9	9
Prednisone	3	6	9
Puricos®	8	1	9
Uni-dur®	3	6	9
Burinex® k	2	6	8
Efexor®	1	7	8
Evista®	0	8	8
Ferrimed®	1	7	8
Oestradiol®	7	1	8
Tegretol®	1	7	8
Zoloft®	0	8	8
Espiride®	5	2	7
Methotrexate	3	4	7
Salazopyrin	2	5	7
Slow-k®	2	5	7
Spiractin®	3	4	7
Alvercol®	4	2	6

Concurrent drug therapy	Subjects without gastroscopy n	Subjects with gastroscopy n	Total n
Bevispas®	3	3	6
Diamicron®	0	6	6
Femigel® pump	0	6	6
Ismo-20®	3	3	6
Plavix®	3	3	6
Puresis®	3	3	6
Serevent®	1	5	6
Trisequens® 28	0	6	6
Unat®	3	3	6
Venteze® complete	6	0	6
Alzam®	3	2	5
Asacol®	1	4	5
Autrin®	1	4	5
Coxflam®	3	2	5
Estrofem® forte 28	5	0	5
Glycomin®	1	4	5
Isordil® sublingual	1	4	5
Lorien®	1	4	5
Panamor®	2	3	5
Sandoz bromazepam®	2	3	5
Singulair®	2	3	5
Stilpane®	5	0	5
Vagifem® vag cream	1	4	5
Ventolin® complete	0	5	5
Xanor®	1	4	5
Zyrtec®	3	2	5
Aldactone®	2	2	4
Azor®	0	4	4

Concurrent drug therapy	Subjects without gastroscopy n	Subjects with gastroscopy n	Total n
Calcicard® sr 240	4	0	4
Detrusitol®	3	1	4
Dormicum®	0	4	4
Eglonyl®	3	1	4
Hexarone® 200	2	2	4
Librax® sc	3	1	4
Molipaxin®	3	1	4
Prozac®	1	3	4
Rivotril®	1	3	4
Telfast®	1	3	4
Zyprexa®	2	2	4
Angitrate®	2	1	3
Arthrexin®	1	2	3
Atrovent®	2	1	3
Azapress®	0	3	3
Berotec® complete	2	1	3
Betoptic® 5ml	0	3	3
Colofac®	2	1	3
Combivent® udv	2	1	3
Dixarit®	2	1	3
Dormonoct®	3	0	3
Flomax® sr	0	3	3
Fybogel orange 3.5g	2	1	3
Imdur®	1	2	3
Kloref®	1	2	3
Luvox® 50	0	3	3
Nivaquine®	2	1	3
Nuzak®	1	2	3

Concurrent drug therapy	Subjects without gastroscopy n	Subjects with gastroscopy n	Total n
Ortho-est®	2	1	3
Pankreoflat®	2	1	3
Paroven®	1	2	3
Rocaltrol®	0	3	3
Sandoz diclofenac®	0	3	3
Slow-mag®	1	2	3
Synapause®	0	3	3
Testosterone®	2	1	3
Tydamine®	1	2	3
Urirex k®	1	2	3
Actonel®	0	2	2
Actraphane®	2	0	2
Arimidex®	0	2	2
Aspirin®	2	0	2
Bactrim® adult	0	2	2
Bayer aspirin cardio®	0	2	2
Be-tabs folic acid®	0	2	2
Carbilev®	0	2	2
Clarityne®	2	0	2
Cosopt ®eye 5ml	0	2	2
Decadron®	2	0	2
Dhea® ecohealth	2	0	2
Diane-35®	2	0	2
Elantan®	2	0	2
Epanutin	1	1	2
Estraderm® tts 100	2	0	2
Evorel ®50	2	0	2
Flomax® sr	2	0	2

Concurrent drug therapy	Subjects without gastroscopy n	Subjects with gastroscopy n	Total n
Foradil®	0	2	2
Glucomed®	0	2	2
Isoptin®	0	2	2
Kliogest®	2	0	2
Kliogest®	0	2	2
Lantanon®	0	2	2
Lentogesic®	1	1	2
Madopar®	2	0	2
Maxolon®	2	0	2
Menograine®	0	2	2
Meticorten®	0	2	2
Microphyllin®	2	0	2
Motilium®	2	0	2
Neurontin®	1	1	2
Nitrolingual ®20ml	2	0	2
Novonorm®	0	2	2
Panado® tracer	0	2	2
Pax®	0	2	2
Pentasa®	0	2	2
Persantin® 200 retard	0	2	2
Petrix ®anti oxidant	0	2	2
Plato®	2	0	2
Postoval®	1	1	2
Prograf ®prc04ksa	0	2	2
Prothiaden®	2	0	2
Purgoxin®	1	1	2
Revellex 1	1	1	2
Sandoz cinnarizine®	0	2	2

Concurrent drug therapy	Subjects without gastroscopy n	Subjects with gastroscopy n	To al n
Sandoz furosemide®	1	1	2
Sandoz zopiclone®	0	2	2
Seroquel®	1	1	2
Sotahexal®	0	2	2
Sporanox®	1	1	2
Synap forte®	2	0	2
Sinemet®	2	0	2
Tambocor®	0	2	2
Tensodol®	2	0	2
Theo-dur®	0	2	2
Timoptol® .5% 5ml	0	2	2
Tramal ®sr	0	2	2
Trental ®400	1	1	2
Tryptanol®	0	2	2
Urbanol®	0	2	2
Veltex® cr	2	0	2
Vit e-1000 iu vitaforce®	0	2	2
Voltaren®	1	1	2
Xalatan ®2.5ml	1	1	2
Xa ral ®sr	1	1	2
Zoladex® depot	0	2	2
Accolate®	1	0	1
Adco-diclofenac®	0	1	1
Adco-indomethacin®	0	1	1
Adco-phenobarb®	1	0	1
Adco-sodasol eff®	0	1	1
Agiolax®	1	0	1
Alapren ®10	0	1	1

Concurrent drug therapy	Subjects without gastroscopy n	Subjects with gastroscopy n	Total n
Alchera®	0	1	1
Allomaron®	1	0	1
Alphosyl®	0	1	1
Angi-spray® 20ml	1	0	1
Antizid®	0	1	1
Aprovel®	1	0	1
Arava®	0	1	1
Arelix®	0	1	1
Artane®	0	1	1
Asthavent® 300	0	1	1
Aterax®	0	1	1
Aurorix®	0	1	1
Beesix®	0	1	1
Beespan®	0	1	1
Androcur®	0	1	1
Be-tabs aspirin ®	0	1	1
Betaferon®	0	1	1
Brexecam®	1	0	1
Bromaze 3®	0	1	1
Brufen®	0	1	1
Casodex®	0	1	1
Cataflam®	0	1	1
Cellcept®	0	1	1
Chela-cal®	0	1	1
Chela-fer®	0	1	1
Climara 50®	0	1	1
Climen®	0	1	1
Colchicine®	0	1	1

Concurrent drug therapy	Subjects without gastroscopy n	Subjects with gastroscopy n	Total n
Combivir®	0	1	1
Convulex®	1	0	1
Covocort®	0	1	1
Cytotec®	0	1	1
Daonil®	1	0	1
Degranol®	0	1	1
Depuran®	0	1	1
Diflucan®	1	0	1
Dilatrend®	1	0	1
Diotroxin®	0	1	1
Duphalac® dry 10g	0	1	1
Edronax®	0	1	1
Effercal-d®	0	1	1
Eldepryl®	0	1	1
Epilim®	1	0	1
Eprex® pref 0.4ml	0	1	1
Estro pause® n	1	0	1
Ethipramine®	0	1	1
Etomine®	0	1	1
Etrafon® d	0	1	1
Etrafon® f	1	0	1
Euphyllin® retard	0	1	1
Exelon®	1	0	1
Ferrous® sulph co	0	1	1
Creon® 25000	0	1	1
Fluanxol®	0	1	1
Geratar®	0	1	1
Halcion®	0	1	1

Concurrent drug therapy	Subjects without gastroscopy n	Subjects with gastroscopy n	Total n
Imuran®	0	1	1
Inderal®	1	0	1
Herceptin®	0	1	1
Intragam® im 5ml	0	1	1
Isopto carpine® 15ml	0	1	1
Kalci® 300	0	1	1
Kestine®	1	0	1
Ketoflam® sr	0	1	1
Lentolith® sr	1	0	1
Leponex®	0	1	1
Lexotan®	0	1	1
Lioresal®	0	1	1
Livostin® eye 4ml	0	1	1
Lopresor®	1	0	1
Loratyne®	1	0	1
Loxiflam®	1	0	1
Lurselle®	1	0	1
Luvox® bi-tabs	1	0	1
Macrodantin® 50	1	0	1
Medrol®	0	1	1
Metamucil® orange	0	1	1
Minidiab®	0	1	1
Movicol®	1	0	1
Nafasol® ec	1	0	1
Neo-mercazole®	1	0	1
Normacol® plus	0	1	1
Normison®	0	1	1
Imovane®	0	1	1

Concurrent drug therapy	Subjects without gastroscopy n	Subjects with gastroscopy n	Total n
Novonorm®	1	0	1
Norton-baclofen®	0	1	1
Nuelin® sa	0	1	1
Nyogel® eye 5g	0	1	1
One alpha®	0	1	1
Orap®	1	0	1
Oxis® turbuhaler	1	0	1
Panafcort®	1	0	1
Pasrin®	1	0	1
Phenobarbitone®	0	1	1
Physiotens®	0	1	1
Ponac®	0	1	1
Posterisan®	0	1	1
Primogyn® depot	0	1	1
Procydin®	0	1	1
Prodium®	0	1	1
Progynova®	0	1	1
Proscar®5	1	0	1
Protensin® m	0	1	1
Prothiaden®	1	0	1
Purata®	0	1	1
Pyridoxine®	0	1	1
Quinine sulphate	1	0	1
Reminyl®	1	0	1
Risperdal®	0	1	1
Rolab-amitriptyline®	0	1	1
Rolab-dothiepin®	0	1	1

Concurrent drug therapy	Subjects without gastroscopy n	Subjects with gastroscopy n	Total n
Sandoz fluoxetine®	0	1	1
Sandoz ibuprofen®	1	0	1
Sandoz piroxicam®	0	1	1
Sandoz spironolactone®	0	1	1
Sandoz theophylline®	0	1	1
Senokot®	0	1	1
Serc®	0	1	1
Servatrin®	1	0	1
Servatrin®	0	1	1
Sibelium®	0	1	1
Sinemet® cr	0	1	1
Spiriva® complete	0	1	1
Stocrin®	0	1	1
Rythmol®	1	0	1
Sustanon®	0	1	1
Symbicord® 120 dose	1	0	1
Symmetrel®	0	1	1
Tarka® sr	1	0	1
Teargel® 10g	0	1	1
Tenston® sa	0	1	1
Tertroxin®	0	1	1
Thaden®	0	1	1
Topamax®	0	1	1
Transact® lat	1	0	1
Trileptal®	0	1	1
Trusopt® owi 5ml	0	1	1
Urispas®	0	1	1
Utrogestan®	0	1	1

Concurrent drug therapy	Subjects without gastroscopy n	Subjects with gastroscopy n	Total n
Venofer® iv 5ml	0	1	1
Vitamin® b12 1ml	1	0	1
Zaroxolyn®	1	0	1
Zometa®	0	1	1
Zomig®	0	1	1
Zopimed®	1	0	1
Zyloprim®	1	0	1

Appendix 4: Ethical clearance

5800471

UNIVERSITY OF KWAZULU-NATAL

RESEARCH OFFICE (FRANCIS STOCK BUILDING)
HOWARD COLLEGE
TELEPHONE NO.: 031 – 2603587

21 FEBRUARY 2005

MR./S. AB SULEMAN
PHARMACY AND PHARMACOLOGY

Dear Mr./s. Suleman

ETHICAL CLEARANCE

I wish to confirm that ethical clearance has been granted for the following project:

"A retrospective analysis of patients who have approved gastro-oesophageal reflux disease (GORD) from a private medical aid fund"

Yours faithfully

MR. PHUMELELE XIMBA
(FOR) MANAGER: RESEARCH OFFICE

PS: The following general condition is applicable to all projects that have been granted ethical clearance:

THE RELEVANT AUTHORITIES SHOULD BE CONTACTED IN ORDER TO OBTAIN THE NECESSARY APPROVAL SHOULD THE RESEARCH INVOLVE UTILIZATION OF SPACE AND/OR FACILITIES AT OTHER INSTITUTIONS/ORGANISATIONS. WHERE QUESTIONNAIRES ARE USED IN THE PROJECT, THE RESEARCHER SHOULD ENSURE THAT THE QUESTIONNAIRE INCLUDES A SECTION AT THE END WHICH SHOULD BE COMPLETED BY THE PARTICIPANT (PRIOR TO THE COMPLETION OF THE QUESTIONNAIRE) INDICATING THAT HE/SHE WAS INFORMED OF THE NATURE AND PURPOSE OF THE PROJECT AND THAT THE INFORMATION GIVEN WILL BE KEPT CONFIDENTIAL.

cc. Director of School
cc. Supervisor

TOTAL P.02

Appendix 5: Permission to access medical aid information

NMP

NATIONAL MEDICAL PLAN

Jan 2004

To whom it may concern

Re: Permission for Dissertation for Aisha Suleman

Topic: Retrospective Analysis of patient who have approved Gastro Oesophageal Reflux Disease (GORD) from a private medical aid fund

National Medical Plan have given permission for this study to be conducted

(2004)

RICHARD PARSONS
CHAIRMAN
NATAL MEDICAL PLAN
5734376

Appendix 6: Medical Aid Fund Reports

Top Ten Chronic Diagnosis
Hypertension
Hyperlipidaemia
Diabetes Mellitus Type I
Diabetes Mellitus Type II
Coronary Artery Disease
Asthma
Epilepsy
Cardiac Failure
Parkinson's Disease
Glaucoma

Appendix 7: Grading systems for endoscopic assessment of oesophagitis

Savary-Miller classification		Los Angeles classification	
Grade	Definition	Grade	Definition
I	Normal oesophageal mucosa	A	One or more mucosal breaks no longer than 5mm, none of which extends between the tops of the mucosal folds
II	Isolated round or linear erosions from the gastro-oesophageal junction, not involving entire circumference	B	One or more mucosal breaks more than 5mm long, none of which extends between the tops of two mucosal folds
III	Confluent erosions extending around the entire circumference or superficial ulcerations without stenosis	C	Mucosal breaks that extend between the tops of two or more mucosal folds, but which involve less than 75 per cent of the mucosal circumference
IV	Erosions and deep ulcers, strictures, or Barrett's oesophagus	D	Mucosal breaks which involve at least 75 per cent of the mucosal circumference
**Note: Individual grades I to IV are not equivalent to individual grades A to D*			

(Kinnear et al., 1999; Dent, 1999)

Appendix 8: Categories of drugs in pregnancy

Category	Definitions*	Clinical Application
Category A	"Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimester), and the possibility of fetal harm appears remote."	For all practical purposes, there is no Category A drugs.
Category B	"Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters)."	Category B drugs include prenatal vitamins, acetaminophen and several other medications used routinely and safely during pregnancy. If there is a clinical need for a Category B drug, it is considered safe to use it.
Category C	"Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus."	Category C drugs have not been shown to be harmful to foetuses (if they had been, they wouldn't be Category C drugs). However, there are some reasons to be more concerned about these drugs than Category B drugs. If the pregnant patient will benefit from a Category C drug, it is generally used, although most obstetricians would prefer a Category B drug if it will give equivalently good results.
Category D	"There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective.)"	Category D drugs have some significant risks. They should be used during pregnancy only when the alternatives are worse.
Category X	"Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant."	Category X drugs should not be used during pregnancy.

*Food and Drug Administration. Federal Register. 1980. 44:37434-67

Appendix 9: Proton Pump Inhibition

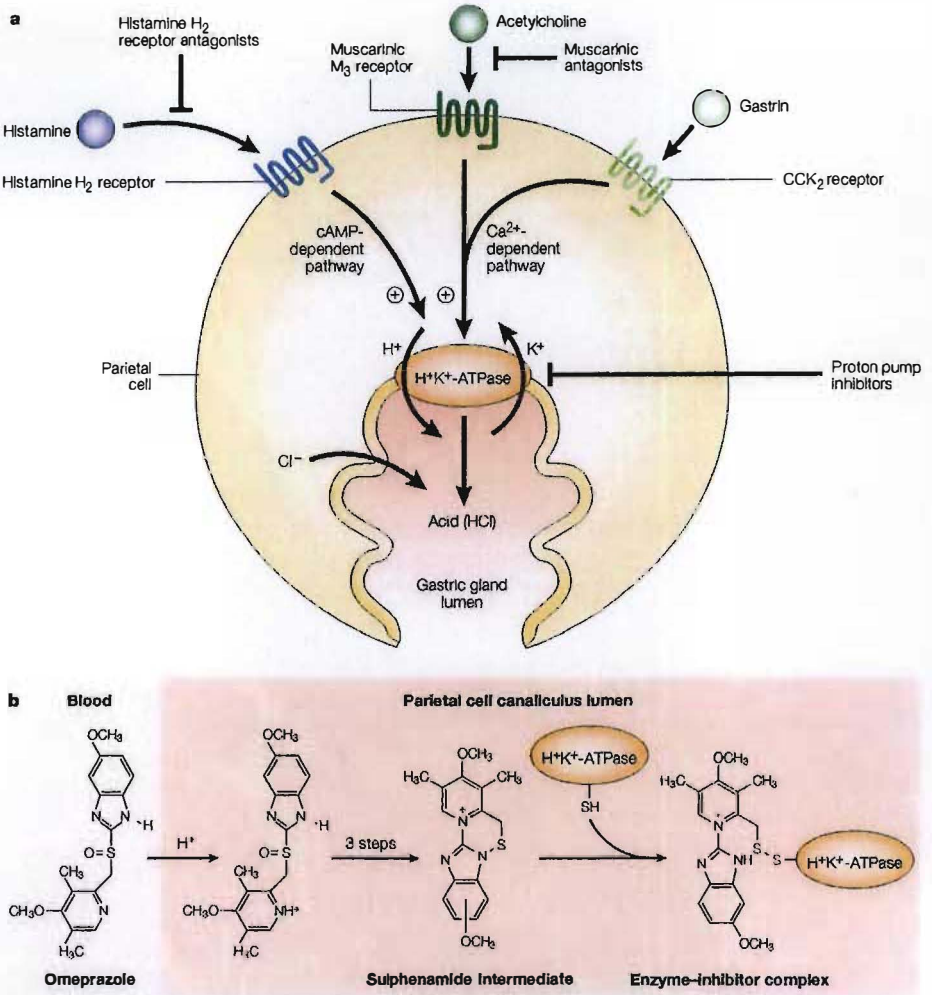

Figure 2 | **Proton-pump inhibition. a** | Gastric acid is secreted by parietal cells of the stomach in response to stimuli such as the presence of food in the stomach or intestine and the taste, smell, sight or thought of food. Such stimuli result in the activation of histamine, acetylcholine or gastrin receptors (the H_2, M_3 and CCK2 receptors, respectively) located in the basolateral membrane of the parietal cell, which initiates signal transduction pathways that converge on the activation of the H^+K^+-ATPase — the final step of acid secretion. Inhibition of this proton pump has the advantage that it will reduce acid secretion independently of how secretion is stimulated, in contrast to other pharmacological approaches to the regulation of acid secretion; for example, the inhibition of acid secretion by H_2 receptor antagonists can be overcome by food-induced stimulation of acid secretion via gastrin or acetylcholine receptors. **b** | Proton-pump inhibitors such as omeprazole are prodrugs that are converted to their active form in acidic environments. Omeprazole is a weak base, and so specifically concentrates in the acidic secretory canaliculi of the parietal cell, where it is activated by a proton-catalysed process to generate a sulphenamide[29]. The sulphenamide interacts covalently with the sulphydryl groups of cysteine residues in the extracellular domain of the H^+K^+-ATPase — in particular Cys 813 — thereby inhibiting its activity[30]. The specific concentration of proton-pump inhibitors such as omeprazole in the secretory canaliculi of the parietal cell is reflected in their favourable side-effect profile.

Drug discovery. Nature Review. 2002. 2:135