Structured management strategy *versus* usual care for gastroesophageal reflux disease: rationale for pooled analysis of five European cluster-randomized trials

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Abstract:

Background: Gastroesophageal reflux disease (GERD) has a major impact at the primary care level and there is a need to evaluate whether the diagnosis and therapeutic management of GERD in Europe needs to be improved.

Methods: This project was designed to test the hypothesis that a new primary care management strategy would improve outcomes for patients with GERD, compared with usual care, in Europe. The analysis pools five separate cluster-randomized studies conducted in Austria, Italy, Norway, Spain and Sweden. These studies used a strategy based on the self-administered GerdQ questionnaire to stratify adult patients with symptoms of heartburn or regurgitation according to the frequency and impact of symptoms. A score of ≥ 8 indicates a high probability of suffering GERD. Patients with a GerdQ impact score ≤ 2 were treated with generic proton-pump inhibitors according to local guidance, and patients with an impact score ≥ 3 were treated with esomeprazole 40 mg once daily.

Results: In total, 2400 patients were enrolled across the five studies. The protocols were modified by individual countries according to their local guidelines/requirements. In Norway, the new management strategy was compared with traditional routine endoscopy and 24-hour pH-metry, and encompassed proton-pump inhibitor reimbursement restrictions. Outcome measures differed by country, but included control of GERD symptoms, self-rated health status and work productivity, treatment changes, specialist referrals and physician adherence. GERD-related use of healthcare resources was also evaluated.

Conclusion: The pooled analysis will determine whether a locally adapted primary care management strategy for GERD, using GerdQ as a patient-tailored diagnostic and therapeutic evaluation tool, is beneficial compared with usual care across five countries with different standard approaches to GERD management and control.

Keywords: gastroesophageal reflux disease, GerdQ, pooled analysis

Introduction

Despite the large and still growing range of treatment options available for gastroesophageal reflux disease (GERD), a significant proportion of patients receiving treatment for this chronic condition remain troubled by their symptoms. This has been shown to cause disruption to their daily lives and has an adverse impact on their quality of life [Gisbert *et al.* 2009a, 2009b; Jones *et al.* 2007]. The socioeconomic cost of

GERD is considerable, as demonstrated by studies of GERD-related lost productivity, use of healthcare resources and the costs of both prescribed and over-the-counter (OTC) medications [Jones *et al.* 2007; Wiklund, 2004]. Moreover, a high proportion (39%) of patients have the more severe form of disrupting GERD, which is associated with significantly poorer quality of life, reduced productivity and increased healthcare resource utilization [Toghiani *et al.* 2010].

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Pharmacological treatment is an essential factor in the management of GERD, but it is not the only one that relates to patient outcomes. The other factors that should be taken into account in clinical practice include the accuracy of diagnosis in primary care, measurement of patient needs as related to the intensity of symptoms and their impact on daily life, and the follow-up plan selected to assess response to the chosen therapeutic strategy. In addition, GERD treatment guidelines and restrictions on reimbursement of drug costs exist in many countries and there are strong national traditions within the management of GERD.

Therefore, we designed the GERD Management Project (GMP) to evaluate the effectiveness of a structured management approach to GERD compared with usual care using pooled individual patient data from five related cluster-randomized trials conducted in Europe. The trials were conducted in Austria, Spain, Italy, Norway and Sweden. In the structured treatment approach, patients were stratified according to symptom severity and treated accordingly, with potent acid suppression reserved for the group with high symptom load. The hypothesis is that such an approach would achieve a better clinical outcome than that achieved through usual clinical practice, but there was sufficient flexibility within the protocol to allow for country-specific adaptations, such that the results will also have meaning within an individual country. By pooling the data from five related studies, we increase the sample size and power to determine the efficacy of the structured approach to GERD management and we will also be able to evaluate the generalizability of study findings across countries.

We describe here the common rationale and design of the studies being conducted in each participating country. Country-specific features of the study designs are presented in Appendix 1.

GMP rationale

The five studies being integrated into GMP (ClinicalTrials.gov identifier: NCT00842387) compare a new management strategy for primary care patients with GERD with existing treatment practice to determine whether clinical outcomes are improved. The new strategy is based upon the use of the self-administered GERD Questionnaire (GerdQ) [Jones *et al.* 2009], a symptom-based diagnosis and management tool for patients with GERD. This validated tool was

constructed following development of 'the Montreal definition', a patient-centred consensus definition of GERD based on symptoms [Vakil *et al.* 2006]. It has been shown to provide a diagnosis of GERD with an accuracy equal to that of a gastroenterologist and thus enables primary care physicians (PCPs) to diagnose and manage GERD with a lower need for referral or endoscopy [Jones *et al.* 2009]. A cut-off score of eight separates patients with a high likelihood of having GERD from those with low, or no likelihood of GERD.

Moreover, use of GerdQ enables patients to be stratified according to the frequency and impact of their symptoms and thus to be treated optimally [Jones *et al.* 2009]. This should both improve patients' health-related quality of life and avoid unnecessary investigation and under- or over-treatment. GerdQ can also be used to follow and measure patients' response to treatment over time.

Because the healthcare systems of the participating countries have different national guidelines for the management of GERD, each study included in GMP was given the flexibility to modify the standard study protocol as needed, in collaboration with local regulatory and healthcare authorities and participating physicians. For example, in Spain and Sweden, a local preference for use of the Reflux Disease Questionnaire (RDQ) tool rather than GerdQ for evaluation of the respective primary endpoints was accommodated. The local modifications incorporated 'real-world' clinical practices in that locality and should facilitate the implementation of the strategy to future clinical practice with a minimum of further refinement.

Features of GMP design by country

Each study was a cluster-randomized, prospective design with a control group conducted in one of five countries: Austria, Spain, Italy, Norway and Sweden. Overall, approximately 2400 patients were included at approximately 69 centres across all studies. GERD management strategies typically differ between countries, and therefore these countries constitute a relevant sample for the evaluation of a standardized, yet adaptable, structured approach to treatment. Country-specific key variations from the standard study protocol are presented in Table 1.

In Austria and Spain, the studies were considered noninterventional by regulatory authorities, and were cluster-randomized for the purpose of assessing the effect of the structured clinical pathway on GERD patients. The implementation of the recommended structured pathway consisted of a specific training session, given by specialists, at a pool of primary care centres, although the decision on whether or not to follow the recommended pathway remained with the individual PCP. This allowed for an estimation of uptake of the recommended pathway, and an assessment of the factors influencing uptake.

In Italy, the study was considered interventional by regulatory authorities, and was run as a PCP level, cluster-randomized, controlled trial comparing a structured clinical pathway *versus* usual care in patients with GERD. The implementation consisted of training sessions on the new clinical pathway.

In Norway, the study was conducted as an evaluation of a symptom-based (GerdQ) *versus* endoscopic approach for the diagnosis, choice of treatment and evaluation of GERD, in which the new structured pathway in the diagnosis and treatment of GERD was compared with the standard clinical pathway.

In Sweden, the study was conducted as an evaluation of the new management strategy for GERD, in which the participating primary care centres were randomized (one to one) to

implementation of the structured clinical pathway or to management of patients according to local clinical routines.

Patients

The patient population in all five studies was representative of primary care patients with symptoms suggestive of GERD, regardless of severity. Men and women aged at least 18 years and capable of understanding and completing the questionnaires were recruited, and informed consent obtained. Patients with alarm symptoms such as dysphagia/odynophagia, anorexia, anaemia, unintentional weight loss, abdominal mass or upper gastrointestinal bleeding were referred for specialist treatment and excluded from the studies. Patients were free to withdraw from the studies at any time, without this affecting their medical care or changing the therapeutic pathway through which they were managed.

Standard study protocol for local adaptation

A schematic representation of the standard study design is presented as Figure 1. Modifications to the standard study protocol were allowed to take account of national guidelines, and key modifications by country are described in Table 1. Key aspects from individual country-specific protocols are listed in Appendix 1.

The standard protocol for use in local adaptation, as required, was as follows: demographic and clinical information was collected for both patient groups (new strategy *versus* standard

Table 1. Key variations from standard protocol.

Country	Protocol variant	Reason for variation
Austria	Second visit 2–3 weeks after baseline, rather than 4 weeks	National guidelines for empirical treatment of GERD + local input from specialists
Spain	RDQ used to evaluate primary study objective, not EQ-5D or WPAI-GERD	Local preference for RDQ No national guidelines on GERD management
Italy	Study classed as interventional due to protocol requirement to administer esomeprazole to patients identified as having 'high impact' GERD	Regulatory requirement National guidelines on GERD management exist, but their implementation is not mandatory
Norway	Gastroenterology specialists selected as investigators, rather than primary care physicians who must refer GERD patients	National GERD guidelines make endoscopic examination ($\pm$ pH-metry) mandatory for reimbursement of treatment costs
Sweden	Extended follow-up of 5 months $\pm$ 4 weeks between Visits 1 and 2 RDQ used to evaluate primary study objective, in addition to the EQ-5D and WPAI-GERD Minor variations in treatment options	Request to measure HRQL and work productivity, before and after treatment Local preference for RDQ GERD guidelines vary on a county-by-county basis

EQ-5D, EuroQol-5D Questionnaire; GERD, gastroesophageal reflux disease; HRQL, health-related quality of life; RDQ, Reflux Disease Questionnaire; WPAI-GERD, Work Productivity and Activity Impairment Questionnaire for patients with GERD.

Figure 1. Standard study flow chart.

care) at the start of the study and with a follow-up visit after 4 weeks to collect efficacy data. Patients who had not improved sufficiently at 4 weeks were reassessed at 8 weeks.

Among primary care centres randomized to the new management strategy, implementation consisted of detailed explanation of the structured approach to physicians, who may use the approach to treat patients at their discretion. The physicians' adherence to the structured clinical pathway was monitored. The physicians in the control groups were informed that the aim of the study was to determine the effect of treatment prescribed to typical GERD patients in usual clinical practice, and that the symptom profile of these patients were to be assessed through questionnaires. To maintain the integrity of randomization, the implementation and control groups did not include centres that were geographically close. Differences in the use of resources between centres that implemented the pathway and those that did not were monitored.

Patient assessments

Patient gender, age, weight, smoking status and alcohol intake were recorded at the study start. Any previous gastrointestinal diagnoses (dyspepsia, hiatus hernia, abdominal pain or peptic ulcer) were also documented.

Patients were classified into different groups according to their GerdQ score. A score of 7 or below indicates that the patient has a low probability of GERD, whereas a score of 8 or higher positions the patient as more likely to be a GERD patient [Jones *et al.* 2009]. Within these two disease levels, patients who had an impact score of

2 or less were classified in the low/moderate impact GERD group, whilst those with a score of 3 or more were classified in the high impact GERD group. Patients with a GerdQ impact score ≤ 2 were treated with generic proton-pump inhibitors according to local guidance, and patients with an impact score ≥ 3 were treated with esomeprazole 40 mg once daily.

Treatment response was determined by the GerdQ score as follows: patients should have a score of less than 2 for each of the items heart-burn, regurgitation, need for OTC treatment and sleep disturbance, on at most 1 day during the previous 7 days.

Other outcomes measures in the original studies varied by country, but generally included: treatment failure, treatment satisfaction, measures of health status and work productivity, safety, and both direct and indirect costs associated with management processes such as physician, specialist and emergency visits, diagnostic tests, surgery and hospitalizations.

Statistical analysis

A pooled analysis based on individual patient data is planned. Mixed regression models will be used to calculate an overall effect estimate (implementation of the structured approach *versus* usual clinical care), taking account of clustering by centre, and adjusted according to baseline differences between intervention and control centres. An analysis stratified by country is also planned. If significant interactions by country are identified, the results for each country will be presented separately. The statistical analysis will be performed using Stata 11 software (StataCorp LP, College Station, TX, USA).

Discussion

We have described here the rationale and design of a project to assess the utility of a new management approach for GERD in primary care, which encompasses major between-country differences in healthcare systems, management approaches and physician preferences. The project was undertaken as an acknowledgement of the importance of evaluating management protocols of patients/diseases in primary care. This is an area that is perhaps under-researched, not only in relation to the evaluation process itself but also in terms of the resultant clinical outcomes.

This project evolved through a unique consultation approach and, in each country, utilized the protocols that were developed and agreed upon following liaison with local healthcare authorities and physicians. This consultative and modifiable approach is a major strength of the project, as it will allow results that are specific to each participating country to be obtained. This aspect will determine whether the GerdQ management tool has real clinical applicability within each country, despite differences in local practice. Evaluation of a new management tool is a complex task and achieving this across a range of regulatory backgrounds and differing national guidelines is a significant achievement. The studies are currently nearing completion or have been completed in each country.

In addition to evaluation of the GerdQ management tool, key data related to disease management costs (new management pathway *versus* usual care) will be generated. A critical factor in assessing the viability of the introduction of the process/protocol is the impact on disease management-related costs. Provision of healthcare costs associated with potential implementation of initiatives intended to improve patient care is a critical requirement for informed decision-making in healthcare administration.

The contribution of a symptom-driven approach, such as the GerdQ management tool, to improved patient outcomes will be evaluated in the context of other management strategies for GERD, such as treatment decisions based largely on endoscopic findings (as currently employed in Norway) and step-up/step-down approaches [Howden *et al.* 2001; Inadomi *et al.* 2001]. It is important to note in this context that the majority of GERD management guidelines support symptom-driven care without recourse to endoscopy for patients with uncomplicated disease (i.e. in the absence of alarm symptoms) [Kahrilas *et al.* 2008; Armstrong *et al.* 2005; DeVault and Castell, 2005].

The results of this project should demonstrate whether or not a locally adapted management strategy for GERD in primary care, based upon GerdQ as a tool in the diagnosis and evaluation of therapy tailored to the needs of the individual patient, is beneficial compared with usual care. The project will therefore provide valuable information on the suitability of GerdQ as a gold standard in the objective diagnosis and monitoring of

patients with disrupting GERD, along with associated disease management costs in relation to usual care.

In summary, if the results show that this management strategy can be successfully adapted to local regulatory procedures and both national and local GERD management guidelines, then the new strategy could be implemented into local clinical practice with minimal further adjustment if it proves to be superior to standard practice.

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Conflict of interest statement

Authors employed by AstraZeneca (MT and JN) participated in study design and management. JP, VG, LA, ET, MG, EG and JGH had full access to all data and had final responsibility for the decision to submit for publication.

References

- Armstrong, D., Marshall, J.K., Chiba, N., Enns, R., Fallone, C.A., Fass, R. *et al.* (2005) Canadian Consensus Conference on the management of gastroesophageal reflux disease in adults - update 2004. *Can J Gastroenterol* 19: 15–35.
- DeVault, K.R. and Castell, D.O. (2005) Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol* 100: 190–200.
- Gisbert, J.P., Cooper, A., Karagiannis, D., Hatlebakk, J., Agreus, L., Jablonowski, H. *et al.* (2009a) Impact of gastroesophageal reflux disease on work absenteeism, presenteeism and productivity in daily life: a European observational study. *Health Qual Life Outcomes* 7: 90.
- Gisbert, J.P., Cooper, A., Karagiannis, D., Hatlebakk, J., Agreus, L., Jablonowski, H. *et al.* (2009b) Impact of gastroesophageal reflux disease on patients' daily lives: a European observational study in the primary care setting. *Health Qual Life Outcomes* 7: 60.
- Howden, C.W., Henning, J.M., Huang, B., Lukasik, N. and Freston, J.W. (2001) Management of heartburn in a large, randomized, community-based study: comparison of four therapeutic strategies. *Am J Gastroenterol* 96: 1704–1710.
- Inadomi, J.M., Jamal, R., Murata, G.H., Hoffman, R.M., Lavezo, L.A., Vigil, J.M. *et al.* (2001)

- Step-down management of gastroesophageal reflux disease. *Gastroenterology* 121: 1095–1100.
- Jones, R., Junghard, O., Dent, J., Vakil, N., Halling, K., Wernersson, B. *et al.* (2009) Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. *Aliment Pharmacol Ther* 30: 1030–1038.
- Jones, R., Liker, H.R. and Ducrotté, P. (2007) Relationship between symptoms, subjective well-being and medication use in gastro-oesophageal reflux disease. *Int J Clin Pract* 61: 1301–1307.
- Kahrilas, P.J., Shaheen, N.J. and Vaezi, M.F. (2008) American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. *Gastroenterology* 135: 1392–1413.
- Toghanian, S., Wahlqvist, P., Johnson, D.A., Bolge, S.C. and Liljas, B. (2010) The burden of disrupting gastro-oesophageal reflux disease: a database study in US and European cohorts. *Clin Drug Investig* 30: 167–178.
- Vakil, N., van Zanten, S.V., Kahrilas, P., Dent, J. and Jones, R. (2006) The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 101: 1900–1920.
- Wiklund, I. (2004) Review of the quality of life and burden of illness in gastroesophageal reflux disease. *Dig Dis* 22: 108–114.

Appendix 1: Agreed local variations from standard protocol

Austria

Patients will have three scheduled visits: baseline, weeks 2–3 (to assess clinical response and enable treatment change or referral to a specialist, if required, as per national guidelines) and weeks 6–8.

Primary objective. The primary objective is to compare the control of GERD symptoms in patients treated at primary care clinics (PCCs) that have or have not implemented the structured pathway. Control of symptoms is to be based on results of the GerdQ, need of treatment change and percentage of patients who require referral to a specialist.

Secondary objectives. The secondary objectives are: to describe the physician adoption rate of the structured pathway in PCCs that implement the pathway; to evaluate the characteristics of the physicians and PCCs that adopt the structured pathway; and to compare resource use in PCCs that either do or do not implement the pathway.

Inclusion/exclusion criteria. Inclusion and exclusion criteria are summarized in Table A1.1.

Study flow. The study flow and study pathway in Austria are summarized in Figures A1.1 and A1.2, respectively.

Table A1.1. Patient inclusion and exclusion criteria for Austria.

Inclusion criteria	Exclusion criteria
Provision of informed consent ≥18 years of age, both genders Presenting with typical symptoms suggestive of GERD (heartburn or regurgitation as prevailing symptoms) of any severity Able to understand and complete the questionnaires	Any condition that, in the investigator's opinion, makes the patient's participation in the study difficult Current participation in another clinical trial
GERD, gastroesophageal reflux disease.

Figure A1.1. Study flow chart for Austria.

Figure A1.2. Study pathway for Austria.

Spain

While national guidelines for the management of GERD exist in Spain, their use is not compulsory. The RDQ assessment tool will be used instead of the EQ-5D or the WPAI-GERD, by local preference.

Primary objective. The primary objective is to assess symptom relief and patient treatment satisfaction in patients with typical GERD who were treated according to either the structured clinical pathway or with usual clinical practice.

Secondary objectives. The secondary objectives are to evaluate physician adherence to the structured treatment pathway and related factors, and to compare the impact of pathway implementation, compared with usual practice, with respect to healthcare resource use and patient referral rates to specialists.

Inclusion/exclusion criteria. Inclusion and exclusion criteria are summarized in Table A1.2.

Study flow. The study flow and study pathway for Spain are summarized in Figures A1.3 and A1.4, respectively.

Table A1.2. Patient inclusion and exclusion criteria for Spain.

Inclusion criteria	Exclusion criteria
Signed informed consent	Alarm symptoms (dysphagia/odynophagia, anorexia, anaemia, unintentional weight loss, abdominal mass, upper gastrointestinal bleeding)
≥18 years of age, both genders	Any condition that, in the investigator's opinion, makes the patient incapable of completing the questionnaires or complying with the study requirements
Presence of typical symptoms suggestive of GERD according to the Montreal definition (heartburn and acid regurgitation as prevailing symptoms that are troublesome for the patient)	Current participation in another clinical trial
Patients should comply with the following criteria:	
• New diagnosis or symptomatic recurrence	
• Received ≤2 doses per week of prescription or OTC PPIs, or H ₂ RA in the past 2 weeks (antacids permitted)	

GERD, gastroesophageal reflux disease; H₂RA, histamine₂-receptor antagonist; OTC, over-the-counter; PPI, proton-pump inhibitor.

Figure A1.3. Study flow chart for Spain.

Figure A1.4. Study pathway for Spain.

Italy

Italian study centres conducted an interventional study for regulatory reasons. National guidelines for the management of GERD in Italy exist, but their use is not mandatory.

Primary objective. The primary objective is to assess and compare GERD symptom control (based on GerdQ results, need of treatment change and the percentage of patients requiring specialist referral) in patients who were treated at centres used either the structured treatment pathway or usual clinical practice.

Secondary objectives. The secondary objective is to investigate the difference in direct healthcare resource consumption at PCCs using the structured treatment pathway and those using usual clinical practice.

Inclusion/exclusion criteria. Inclusion and exclusion criteria are summarized in Table A1.3.

Randomization. A stratified technique will use a random-number generator to produce a balanced distribution of PCPs across intervention groups. The randomization list will be obtained using the SAS PLAN Procedure (SAS/STAT version 9.1).

Study flow. The study flow and study pathways are summarized in Figures A1.5 and A1.6, respectively.

Table A1.3. Patient inclusion and exclusion criteria for Italy.

Inclusion criteria	Exclusion criteria
Signed informed consent	Documented medical history or GI pathology such as: <ul style="list-style-type: none">• GI malignancy• Zollinger–Ellison syndrome or malabsorption• Significant concomitant disease as judged by the investigator to interfere with the evaluation of the study
≥18 years of age, both genders	Documented upper GI surgery (<i>previous lower GI surgery such as appendectomy, colonic resection, cholecystectomy, or gynaecological surgery are not exclusion criteria</i>)
Patients presenting with typical symptoms suggestive of GERD (heartburn or regurgitation as prevailing symptoms) of any severity and frequency	Presence of IBS. This is characterised by chronic or recurrent abdominal pain associated with a chronic or recurrent bowel disturbance and/or bloating, that in the opinion of the investigator is likely to be due to IBS, or ≥2 of the following criteria: <ul style="list-style-type: none">• Visible abdominal distension• Pain relieved by a bowel action• More frequent stools with the onset of pain• Looser stools with onset of pain• Rectal passage of mucus• A sensation of incomplete defecation
Patients should comply with the following criteria: <ul style="list-style-type: none">• New diagnosis or symptom relapse• No treatment with PPIs or H₂RAs or a maximum of two doses a week in the past 2 weeks, allowing treatment with antacids• Able to understand and complete the questionnaires	Requirement for continuous concurrent therapy with the following medications during the study period: sucralfate, quinidine, warfarin and other vitamin-K antagonists, phenytoin, biphosphonates, methotrexate, antidepressants (≥3 days per week), prostaglandin analogues, ketoconazole, fluconazole, itraconazole, diazepam, cisapride, NSAIDs or ASA (>300 mg/day)
	Pregnancy or lactation
	Chronic alcoholism, drug abuse or psychological condition judged by the primary care physician to potentially result in poor subject compliance or interfere with study evaluation
	Suspected or confirmed current malignancy, except basal cell carcinoma
	Known hypersensitivity to PPIs or any of their constituents
	Participation in a clinical study during the preceding 90 days

ASA, acetylsalicylic acid; GERD, gastroesophageal; GI, gastrointestinal; H₂RA, histamine₂-receptor antagonist; IBS, irritable bowel syndrome; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton-pump inhibitor.

Figure A1.5. Study flow chart for Italy.

Figure A1.6. Study pathway for Italy.

Norway

The study recruited patients who are referred from primary care to gastroenterology specialists due to symptoms suggestive of GERD but with no alarm symptoms, and will be conducted in accordance with national GERD management guidelines.

The study compared patient care using diagnosis and management according to GerdQ score (threshold for initiating esomeprazole treatment is GerdQ total score ≥ 8 and GerdQ impact score ≥ 4) *versus* care based on findings during upper gastrointestinal endoscopy and/or 24-hour pH-metry; these investigations are required for eligibility for reimbursement of acid-suppressive treatment, with subsequent (PPI) use according to the local preferred product scheme.

Primary objective. The primary objective is to compare treatment response and symptomatic control in patients with GERD using the GerdQ for diagnosis and initial treatment (new structured pathway) *versus* treatment following current local practice (ordinary clinical pathway).

Secondary objectives. The secondary objectives are to compare cost-effectiveness (direct and indirect costs), health status (EQ-5D scores) and work productivity (WPAI-GERD scores), and to summarize patients with verified upper gastrointestinal organ damage during the study period in both treatment pathways.

Inclusion/exclusion criteria. Inclusion and exclusion criteria are summarized in Table A1.4.

Randomization. Patients were sequentially assigned unique randomization codes from a list generated by a computer program at AstraZeneca.

Study flow. The study flow and structured and standard study pathways are summarized in Figures A1.7, A1.8 and A1.9, respectively.

Table A1.4. Patient inclusion and exclusion criteria for Norway.

Inclusion criteria	Exclusion criteria
Signed informed consent	Major health condition(s) that precludes participation, as judged by the investigator
≥18 years of age, both genders	Alarm symptoms, defined as unintentional weight loss, severe or progressive dysphagia, and upper GI bleeding
Patients presenting with typical symptoms suggestive of GERD (heartburn or acid regurgitation as predominant symptoms), referred to or followed-up by a gastroenterologist	Use of more than 2 doses per week of PPI, H ₂ RA or antacids within the preceding 2 weeks
Able to understand and complete the questionnaires	Endoscopic and/or pH-metry examination within the previous year
	Previous upper GI surgery
	Participation in any clinical study within the defined treatment period

GERD, gastroesophageal reflux disease; GI, gastrointestinal; H₂RA, histamine₂-receptor antagonist; PPI, proton-pump inhibitor.

Figure A1.7. Study flow chart for Norway.

Figure A1.8. Structured pathway for Norway.

Figure A1.9. Standard pathway for Norway.

Sweden

The management guidelines for GERD differ from county to county in Sweden. The study was therefore designed to allow participating centres the choice of therapy according to local guidelines. At PCCs that are randomized to implement the new management pathway, patient eligibility for inclusion will be determined by GerdQ score. Centres randomized to provide treatment according to local clinical practice will include patients regardless of their GerdQ score.

Patient visits are to be scheduled at baseline and 5 months (± 4 weeks). Follow-up time will be extended in order to measure health-related quality of life and work productivity before and after treatment. The RDQ tool will be used, by local preference, in addition to the EQ-5D and WPAI-GERD.

Primary objective. The primary objective is to compare the clinical outcome of patients treated with the structured clinical pathway *versus* those treated with therapy according to local guidelines, with regard to total symptom relief as measured by the RDQ. To be considered as symptom free according to RDQ, the patient may only experience mild symptoms on one day during the preceding week.

Secondary objectives. The secondary objectives are to:

- to compare the proportion of patients with persistent symptoms according to GerdQ in the two groups;
- to compare the use of healthcare resources in the two groups between study visits;
- to describe the impact of symptoms on patients' daily life, using the EQ-5D;
- to describe the impact of reflux symptoms on work productivity, using the WPAI-GERD;
- to document the reason(s) for the patient consultation at baseline;
- to describe the changes in treatment in order to obtain more efficient acid inhibition;
- to describe resource consumption between study visits;
- to describe the patients' experience of treatment/care given during the study;
- to explore other GERD-related symptoms in the two groups;
- to explore the investigators' confidence in the management of GERD patients in the two groups after participation in the study.

Inclusion/exclusion criteria. Inclusion and exclusion criteria are summarized in Table A1.5.

The number of patients enrolled in each centre has been selected to be 10 subjects, for practical reasons, including the likelihood of finding centres that can allocate the time needed for the study and provide sufficient patients. Other studies in this therapeutic area have had similar numbers of patients from each centre.

A total of 110 patients are required to perform a two-group χ^2 test with a 0.05 two-sided significance level that will have 80% power to detect the difference between two groups, one detecting 90% and the other detecting 75% of the patients free of symptoms according RDQ, with a 10% allowance for loss to follow up.

Study flow. The study flow and the study pathways for patients with GERD symptoms who had not received treatment previously and for those who had symptoms despite PPI treatment are summarised in Figures A1.10, A1.11 and A1.12, respectively.

Table A1.5. Patient inclusion and exclusion criteria for Sweden.

Inclusion criteria	Exclusion criteria
Signed informed consent	Prophylactic PPI use to reduce the risk of ulcers in patients being treated with NSAIDs
≥18 years of age, both genders	PPI treatment to heal an ulcer induced by NSAID treatment
Presenting with typical symptoms suggestive of GERD (heartburn or regurgitation as prevailing symptoms) of any severity, with or without ongoing PPI treatment	PPI treatment for <i>Helicobacter pylori</i> eradication
Patients at centres following the clinical structured pathway must either obtain a score >8 according to GerdQ or, if already on treatment for GERD, show any indication of insufficient GERD treatment according to GerdQ	PPI treatment for peptic ulcer
Able to understand and complete the questionnaires	Continuous use of H ₂ RA
	Current participation in another clinical trial
GERD, gastroesophageal reflux disease; GerdQ, GERD Questionnaire; GI, gastrointestinal; H ₂ RA, histamine ₂ -receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton-pump inhibitor.

Figure A1.10. Study flow chart for Sweden.

Figure A1.11. Study pathway for Swedish patients with GERD who had not received previous treatment.

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Figure A1.12. Study pathway for Swedish patients with GERD symptoms despite PPI therapy.