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Federal Department of Home Affairs
Federal Office of Public Health FOPH
Health and Accident Insurance Directorate
Section Health Technology Assessment

Health Technology Assessment (HTA)

HTA Scoping Report

Title	Treatment of non-erosive gastroesophageal reflux disease patients with proton pump inhibitors
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Technology	Proton pump inhibitors
Date	30-09-2019
Type of Technology	Pharmaceuticals
Keywords	Proton pump inhibitor (PPI), gastroesophageal reflux disease (GERD, GORD), erosive reflux disease (ERD), non-erosive reflux disease (NERD), on-demand PPI therapy, continuous PPI therapy, de-prescribing, step-down approach

Executive Summary:

The cost-effectiveness of PPI continuous long-term therapy in adult non-erosive reflux disease (NERD) and uninvestigated GERD (gastroesophageal reflux disease) patients has been questioned.

Proton pump inhibitor (PPI) therapy is typically prescribed for gastroesophageal reflux disease (GERD) patients with symptoms such as heartburn and/or acid regurgitation. First-line empiric treatment is prescribed for 4-8 weeks in patients without alarm symptoms (for example, weight loss and anaemia). If symptoms do not disappear after this treatment, further diagnostic tests (endoscopy and/or pH monitoring) can be performed to distinguish erosive from non-erosive reflux disease (ERD and NERD) patients. Long-term continuous or on-demand PPI treatment is prescribed for diagnosed NERD patients and GERD patients that are not investigated by endoscopy.

The aim of this scoping report is to determine the feasibility of conducting a Health Technology Assessment evaluation comparing efficacy, effectiveness, safety and cost-effectiveness of long-term continuous versus on-demand PPI treatment in adult NERD patients and uninvestigated GERD patients.

Systematic searches were performed in PubMed (MEDLINE), Embase.com and other complementary databases to identify relevant published efficacy, effectiveness, safety and cost-effectiveness

evidence. Additional literature was searched for information on potential relevant social, legal, ethical and organisational aspects related to the topic.

Six articles, reporting on five randomised controlled trials, comparing long-term continuous PPI treatment with long-term on-demand PPI treatment were selected to address the efficacy and safety of the treatment. Three of these trials were on endoscopically uninvestigated GERD population and the remaining two were on NERD population.

Nine articles were selected to address the cost-effectiveness of the treatment. Four of these nine articles were trial-based economic evaluations (three on uninvestigated GERD and one on NERD population) and the remaining five studies were model-based economic evaluations (two on uninvestigated GERD and three on NERD population).

The searches on legal, organisational, social and ethical issues did not yield relevant studies.

Trial-based economic evaluations do not provide sufficient evidence on the cost-effectiveness of long-term continuous versus on-demand PPI treatment in Switzerland. A de novo economic model may be required if a full HTA report is commissioned.

Overall, the evidence base is considered sufficiently large to conduct a full HTA assessment.

Zusammenfassung:

Die Kosteneffizienz der kontinuierlichen Langzeittherapie mit Protonenpumpeninhibitoren (PPI) bei erwachsenen Patientinnen und Patienten mit nicht erosiver Refluxerkrankung (NERD) oder nicht endoskopisch untersuchter gastroösophagealer Refluxerkrankung (GERD) wurde in Frage gestellt.

Die Therapie mit PPI wird typischerweise bei Patientinnen und Patienten mit GERD verschrieben, die Symptome wie Sodbrennen und/oder saures Aufstossen aufweisen. Die empirische Erstlinienbehandlung wird bei Patientinnen und Patienten ohne Alarmsymptome (z.B. Gewichtsabnahme und Anämie) für 4–8 Wochen verschrieben. Wenn die Symptome nach dieser Behandlung nicht abklingen, können weitere diagnostische Tests (Endoskopie und/oder pH-Überwachung) durchgeführt werden, um erosive von nicht erosiven Refluxerkrankungen (ERD und NERD) zu unterscheiden. Eine kontinuierliche oder bedarfsgerechte Langzeittherapie mit PPI wird für diagnostizierte NERD-Patient/innen und nicht endoskopisch untersuchte GERD-Patient/innen verschrieben.

Ziel dieses Scoping-Berichts ist, die Durchführbarkeit einer Gesundheitstechnologiebewertung (Health Technology Assessment, HTA) zu ermitteln, bei der die Wirksamkeit, Effektivität, Sicherheit und Kosteneffizienz einer kontinuierlichen PPI-Langzeittherapie bei erwachsenen NERD-Patient/in-

nen und nicht endoskopisch untersuchten GERD-Patient/innen im Vergleich mit einer PPI-Behandlung nach Bedarf (On Demand) geprüft wird.

Zu diesem Zweck wurden systematische Literaturrecherchen in PubMed (MEDLINE), Embase.com und anderen komplementären Datenbanken durchgeführt, um relevante publizierte Evidenz für die Wirksamkeit, Effektivität, Sicherheit und Kosteneffizienz zu ermitteln. Zusätzliche Literatur wurde nach Informationen zu potenziell relevanten sozialen, rechtlichen, ethischen und organisatorischen Aspekten im Zusammenhang mit dem Thema durchsucht.

Sechs Artikel, die fünf randomisierte kontrollierte Studien beschreiben, welche die kontinuierliche Langzeittherapie mit der On-Demand-Langzeittherapie vergleichen, wurden ausgewählt, um die Wirksamkeit und Sicherheit der Behandlung zu untersuchen. Drei dieser Studien wurden an nicht endoskopisch untersuchten GERD-Patientengruppen durchgeführt, und die restlichen zwei an NERD-Patientengruppen.

Neun Artikel wurden ausgewählt, um die Kosteneffizienz der Behandlung zu untersuchen. Vier dieser neun Artikel waren studienbasierte ökonomische Bewertungen (drei zu nicht endoskopisch untersuchten GERD-Patient/innen und eine zu NERD-Patient/innen), und bei den restlichen fünf Studien handelte es sich um modellbasierte ökonomische Bewertungen (zwei zu nicht endoskopisch untersuchten GERD-Patient/innen und drei zu NERD-Patient/innen).

Die Recherchen zu rechtlichen, organisatorischen, sozialen und ethischen Fragen ergaben keine relevanten Studien.

Studienbasierte ökonomische Evaluationen liefern keine ausreichenden Hinweise auf die Kosteneffizienz einer kontinuierlichen PPI Langzeittherapie im Vergleich zur PPI-Einnahme on Demand in der Schweiz. Ein neues ökonomisches Modell kann erforderlich sein, wenn ein vollständiger HTA-Bericht in Auftrag gegeben wird.

Insgesamt wird die Evidenzgrundlage als ausreichend erachtet, um eine vollständige HTA-Bewertung durchzuführen.

Résumé:

Le ratio coût-efficacité du traitement au long cours par inhibiteurs de la pompe à protons (IPP) en continu chez des patients adultes souffrant d´un reflux gastro-œsophagien non-érosif (NERD) ou d´un reflux gastro-œsophagien n'ayant pas fait l'objet d'un examen par endoscopie (GERD) est contesté.

Les IPP sont principalement prescrits aux patients souffrant de reflux gastro-œsophagien (RGO)

symptomatique (pyrosis et/ou régurgitations acides). Un traitement de première ligne est prescrit pendant quatre à huit semaines pour les patients sans symptômes évoquant une œsophagite compliquée (perte de poids et anémie, par exemple). Si les symptômes ne disparaissent pas après ce traitement, on procède à d'autres examens (endoscopie et/ou pH-métrie) afin de déterminer si les patients ont une œsophagite érosive (ERD) ou non-érosive (NERD). La prise d'IPP au long cours, en continu ou à la demande, est indiquée pour les patients diagnostiqués comme NERD ainsi que pour les patients souffrant d'un RGO mais n'ayant pas fait l'objet d'une exploration endoscopique.

L'objet de ce rapport est de déterminer la faisabilité de la réalisation d'une évaluation des technologies de la santé (Health Technology Assessment, HTA) comparant l'efficacité (efficacy), l´efficacité en conditions réelles (effectiveness), la sûreté et le rapport coût-efficacité d'un traitement par IPP au long cours en continu par rapport à la demande, chez des patients adultes diagnostiqués comme NERD et chez des patients souffrant d'un RGO n'ayant pas fait l'objet d'un examen par endoscopie.

Une revue systématique a été entreprise sur PubMed (MEDLINE), Embase.com et d'autres bases de données complémentaires afin d'identifier les données publiées sur l'efficacité, l´efficacité en conditions réelles, la sureté et le ratio coût-efficacité des traitements par IPP pour les populations d'intérêt. Une recherche documentaire complémentaire a été menée sur les potentiels enjeux légaux, organisationnels, sociaux et éthiques de ces traitements.

Concernant l'efficacité clinique, six articles ont été identifiés, faisant état de cinq essais randomisés en double aveugle comparant deux schémas de traitement au long cours par IPP, l'un en continu, l'autre à la demande. Trois de ces essais incluent des patients dont le RGO n'avait pas été exploré par endoscopie, au contraire des deux autres incluant des patients avec une œsophagite non-érosive.

La recherche de données médico-économiques sur le traitement a permis d'identifier neuf articles. Quatre de ces neuf articles rapportent des évaluations médico-économiques fondées sur des essais (trois concernant des RGO non explorés, un concernant une population de patients présentant un RGO non-érosif); les cinq études restantes correspondent à des évaluations médico-économiques fondées sur un modèle (deux concernant des RGO non explorés, trois portant sur une population de patients présentant un RGO non-érosif).

Les recherches portant sur des problématiques légales, organisationnelles, sociales et éthiques n'ont pas donné de résultats pertinents.

Les évaluations économiques fondées sur des essais n'ont pas permis de fournir des éléments de preuve suffisants sur le rapport coût-efficacité d'un traitement au long cours par IPP en continu en

comparaison avec la demande en Suisse. Un nouveau modèle économique pourrait s'avérer nécessaire si une évaluation des technologies de la santé était commandée.

Globalement, la base de preuves est considérée comme suffisamment large pour réaliser une HTA complète.

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Abbreviations and Acronyms

BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost-Effectiveness
CHF	Swiss Franc
e.g.	exempli gratia (for example)
ERD	Erosive Reflux Disease
FOPH	Federal Office of Public Health
GERD	Gastroesophageal Reflux Disease
GOS	Global Overall Symptom
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GSAS	GERD Symptoms Assessment Scale
GSRS	Gastrointestinal Symptom Rating Scale
HAS	Haute Autorité de Santé (French National Authority for Health)
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
H2RAs	Histamine-Receptor Antagonists
ICER	Incremental Cost-Effectiveness Ratio
i.e.	id est (that is)
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
iMTA	Institute for Medical Technology Assessment
LY	Life Years
MEMS	Medical Event Monitoring System
MESH	Medical Subject Headings
NA	Not Applicable
NERD	Non-Erosive Reflux Disease
NHS	National Health Service
NHS/EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NR	Not Reported
OTC	Over The Counter
OTE	Overall Treatment Evaluation Questionnaire

PAGIQOL	Patient Assessment of upper Gastrointestinal disorders - Quality of Life questionnaire
PBAC	Pharmaceutical Benefits Advisory Committee
PICO	Patients, Intervention, Comparator, Outcome
PPI	Proton Pump Inhibitor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSSRU	Personal Social Services Research Unit
QALYs	Quality-Adjusted Life Years
QoL	Quality of Life
QOLRAD	Quality of Life in Reflux and Dyspepsia Instrument
RCT	Randomised Controlled Trial
SD	Standard Deviation
UK	United Kingdom
ZiN	Zorginstituut Nederland (National Health Care Institute)

Objective of the HTA Scoping Report

The Federal Office of Public Health (FOPH) is reviewing the public reimbursement of PPI continuous long-term therapy in adult non-erosive reflux disease (NERD) and uninvestigated GERD (gastroesophageal reflux disease) patients because its cost-effectiveness has been questioned.

In the scoping phase, 1. long-term continuous (intervention) and 2. long-term on-demand (comparator) use of proton pump inhibitors for non-erosive reflux disease and endoscopically uninvestigated gastroesophageal reflux disease are examined and a central research question is presented based on a systematic review of the literature. In addition, operational key questions are formulated, in order to determine the full scope of the HTA report. The target population, the appropriate comparator and the relevant health outcomes are defined.

Based on the quantity and quality of the identified evidence, the feasibility of a full HTA is assessed by the Federal Office of Public Health and it will be decided whether a full HTA report is going to be commissioned for this topic or not.

1. Medical Background

Gastroesophageal reflux disease (GERD) describes a spectrum of different reflux diseases, including non-erosive reflux disease (NERD), erosive reflux disease (ERD) and complicated forms such as ulcer, columnar metaplasia, stricture and Barett's oesophagus.[1] In the Western world, GERD affects 10-20% of the people. The prevalence of GERD in Switzerland is similar to other industrialised countries and has been estimated to be approximately 18%.[2] More men than women are diagnosed with ERD and more women than men are diagnosed with NERD.[3] NERD is the most frequent diagnosed GERD (50-70%).[1]

In the majority of patients, GERD is not the result of a single underlying pathology, but arises from the interaction of several anatomical and physiological factors.[4] GERD is characterised by reflux of gastric contents into the oesophagus (minimal 1 to 2 times per week), which may lead to oesophageal injury and, in long-term, to oesophageal adenocarcinoma.[1 5 6] GERD can be further classified as the presence of symptoms without oesophageal mucosal erosions/breaks on endoscopic examination (non-erosive disease or NERD) or GERD symptoms with erosions present at conventional endoscopy.[3] In 10% of ERD patients, pre-cancerous Barrett's oesophagus is found.[7] Common initial symptoms of the disease are a burning sensation in the chest (heartburn) and acid regurgitation.[5]

GERD is typically diagnosed by the evaluation of clinical symptoms and the response to acid suppression. Additional diagnostic procedures include upper endoscopy and oesophageal pH monitoring.[8] The 'test and treat' regimen without an endoscopy has both advantages and disadvantages. It allows clinicians to treat the patient immediately, helps to alleviate symptoms, increase patients' satisfaction and quality of life, and reduces the overall economic burden of the cost of endoscopies. Caution is needed however, because there will be a very small number of patients with possible serious disease, which is masked through the treatment of symptoms alone.[9]

The main goal of GERD therapy is the control of symptoms, the healing of esophagitis (if present) and the prevention of complications (i.e. stricture, Barrett's oesophagus and oesophageal adenocarcinoma).[1] Symptomatic (or endoscopic) relapse is very frequent and it has been estimated that 80% of patients have esophagitis relapse after 6 to 12 months; most patients therefore need long-term antisecretory therapy.[1] First-line therapy consists of lifestyle modifications and medical treatment. For a subset of patients, surgical interventions are needed. Several classes of medications exist, including antacids, histamine-receptor antagonists (H_2RAs) or proton pump inhibitors (PPIs).[8]

A turning point in the medical treatment of GERD was the introduction of the first PPI (omeprazole) in 1989. PPIs were initially developed in the late 1970s and early 1980s for the treatment of gastric and duodenal ulcers. The superior efficacy of PPIs in GERD depends on their ability to elevate gastric pH

substantially. PPIs are now one of the most commonly prescribed class of medications in the primary care setting and a major advance in the treatment of GERD.[4] In Switzerland, prescription of PPIs results in considerable costs (CHF 176 million in 2017, Santésuisse), which has to be fully covered by the health insurance.

The management options in terms of use of PPIs are either daily therapy (i.e. maintenance or continuous therapy), intermittent courses of (continuous) therapy, or symptom-driven on-demand therapy.[4] Intermittent therapy is a strategy whereby a patient is given daily treatment in blocks of treatment of fixed duration to relieve symptoms, typically with a duration of 2 to 4 weeks. Treatment is started when symptoms recur during a relapse and is stopped when the patient becomes asymptomatic once again.[10] With on-demand therapy, one dose of PPI is taken only when symptoms occur.[10]

Considerable clinical experience with PPIs endorses their efficacy and safety with long-term use. However according to Pace & Porro, public health authorities, third-party payers, and a proportion of patients expressed concerns about the cost and/or inconvenience of continuous maintenance treatment with PPIs.[11] This has led to the evaluation of different long-term management strategies. These include various “step-down” approaches, including a switch to a cheaper agent (e.g. an H_2RA), or to non-continuous PPI therapy (e.g. alternate days, intermittently, or on-demand).[11] This HTA scoping report will focus on the comparison, (in terms of efficacy, effectiveness, safety and cost-effectiveness[a]) of continuous PPI long-term therapy versus on-demand PPI long-term therapy in adult patients with NERD or uninvestigated GERD. Long-term is defined as therapy taken during a period of six months to five years.

2. Technology

2.1 Technology Description

PPIs are a group of drugs whose aim is to reduce the stomach acid production enduringly and distinctively. PPIs mechanism of action is to irreversibly block the activated hydrogen/potassium adenosine triphosphatase enzyme system (proton pumps in the gastric parietal cells), which secrete hydrochloric acid into the gastric lumen. PPIs are given orally and are absorbed from the small intestine and carried by the blood stream to the gastric parietal cells. PPIs do not act immediately, for optimal efficacy, PPIs have to be dosed before meals (30–60 minutes prior to the first meal).[12]

[a] In this scoping document, the formal FOPH definitions for efficacy, effectiveness and safety will be used.

PPI therapy is prescribed to GERD patients with symptoms such as heartburn and/or acid regurgitation. This first-line empiric treatment is typically given for 4 to 8 weeks. If symptoms do not disappear after this treatment, further diagnostic tests (endoscopy and/or pH monitoring) can be performed.[8]

In ERD patients, discontinuation of the initial PPI therapy often results in a relapse of symptoms. Therefore, continuous PPI long-term therapy at the minimal efficacious dose is typically prescribed for these patients.[8] Continuous PPI long-term therapy is also prescribed for uninvestigated GERD and NERD population, as well. Nevertheless, it has been shown that approximately 30-80% of all GERD patients take PPIs intermittently or on-demand instead of continuously, as initially prescribed.[13-15] NERD patients may be managed with on-demand PPI long-term treatment[1 8 15 16] and it has been reported that these patients take on average one PPI pill in every 3-4 days, which corresponds to ≥ 120 tablets per year.[17 18]

PPIs are associated with few side effects.[19] PPI intolerance has been observed in 1 to 3% of the population (mostly headache, abdominal pain, diarrhoea, flatulence, dyspepsia, and in some rare cases, rash and allergy).[14]

Given their uncontroversial efficacy, effectiveness and the positive safety profile, PPIs are possibly overprescribed.[19] The overutilisation of PPIs in ambulatory care settings is often a result of failure to re-evaluate the need for continuation of therapy, or insufficient use of on-demand and step-down therapy. Prescription of PPI continuous therapy instead of on-demand therapy may contribute to this perception.[18]

Lee et al.[20] reported that 26 to 71% of GERD patients could be managed without continuous PPI long-term medication. Their statement was based on the evidence generated from the systematic review of randomised and non-randomised clinical trials. However, it should be noted that these conclusions are based on patients' reporting of their symptoms and their level of willingness to continue on less intensive therapy rather than on formal assessments of quality of life (QoL).

2.2 Alternative Technologies

Alternative first-line GERD treatments include antacids and H_2RAs. Over-the-counter (OTC) antacids are very common during the first manifestations of the disease. Patients tend to visit a medical doctor only when symptoms increase or persist. OTC antacids have shown to be effective in only approximately 25% of patients with GERD. Similarly, H_2RAs are available over the counter or by prescription. Patients with persistent symptoms after continuous H_2RA treatment are often switched to PPI therapy.[21]

3. Systematic Search Strategy

3.1 Databases and Search Strategy

3.1.1 Efficacy, Effectiveness and Safety

Search strategy

The core of the efficacy, effectiveness and safety systematic review was a PubMed (MEDLINE) literature search complemented with a search in Embase.com. The searches were built using the PICO-framework (see section 5.5). Given the various outcomes of interest, it was decided to keep the search broad; only search strings on 'Patient' and 'Intervention' were included. The applied search filters were time period (2008-2018) and the language of the publications (English). Furthermore, animal studies, case reports and non-pertinent publication types (e.g. editorials, letter, and comments) were excluded with additional search strings. The original search was run on 11 July 2018. During the process, three amendments were made to the search strategy. First, generic PPI brand names of the most common PPIs were included as a search string (search date: 21 August 2018). Second, the time frame of the search was extended to 2000-2007 (search date: 27 August 2018). Thirdly, an additional search was conducted for three non-English languages, namely Dutch, French, and German (search date: 2 October 2018). The details of the search strategies are included in Appendix 9.1. The database output, including all indexed fields per record (e.g. title, authors, abstract), was exported to Endnote version X7.4, where the hits were de-duplicated.

Selection procedure

From the articles retrieved from PubMed (MEDLINE) and Embase.com the relevant references were selected by a two-step selection procedure, based on:

1. Screening of title and abstract: this step yielded the articles that were assessed in full-text. The major topics of the articles were assessed on relevancy for the objectives by the title and abstract. In this step, articles that seemed to contain relevant data for the objectives were selected for full-text screening, while articles that did not seem to contain relevant data were not selected for full-text assessment.
2. Screening of full article: the articles selected during the first phase were assessed in full-text. PDF-files of the original articles were downloaded and stored. Articles were included if the reported information was relevant, based on the inclusion and exclusion criteria, and of sufficient quality and sample size.

The process of selection and inclusion and exclusion of articles was registered in an Endnote library by one of the researchers. The exclusion criteria applied in the selection procedure are reported in the PRISMA flow chart.

Inclusion and exclusion criteria

The list of inclusion and exclusion criteria applied during the selection process is presented in Table 1.

Table 1: Inclusion and exclusion criteria for the efficacy, effectiveness and safety systematic review

	Inclusion	Exclusion
Period publication	• 2000-2018	
Language of publication	• English • Dutch • French • German	• All other languages
Country of study	• All countries	
Study design/type	• RCTs • Non-randomised controlled studies (i.e. non-randomised controlled trials, cohort studies, case-control studies)	• Meta-analysis/systematic review[1] • Narrative review • Cross-sectional studies • Case reports • Non-pertinent publication types (e.g. expert opinion, letter to editor, editorial, comment)
Study quality		No exclusion based on study quality
Study population	• Patients ≥18 years with NERD • Patients ≥18 years with uninvestigated GERD	• Healthy population • Population with other diagnosis than NERD/ uninvestigated GERD • Patients <18 years • GERD population who had prior endoscopy • Population with erosive reflux esophagitis • Population with NERD and erosive reflux esophagitis, without stratification of the results • Patients without initial continuous PPI treatment of 4 to 8 weeks to establish optimal symptom control, before randomisation in the continuous and on-demand PPI therapy arms
Study intervention	• Continuous (daily) PPI long-term therapy (i.e. 6 months to 5 years) with the minimal efficacious dose	• All other interventions • PPI short-term therapy (i.e. <6 months)
Study comparison	• On-demand PPI long-term therapy (i.e. 6 months to 5 years) on 30-50% of the days per year with the minimal efficacious dose	• All other comparisons (e.g. placebo, PPI with another dose, other PPI) • PPI short-term therapy (i.e. <6 months)
Study outcomes	• See outcomes in PICO table (section 5.5) • Other possibly relevant outcomes, but not included in the PICO table (see section 4.1)	

[1] Relevant meta-analyses and systematic reviews were selected during the screening of title and abstract phase. During the full-text phase, reference lists of these meta-analyses and systematic reviews were checked for possibly missed relevant individual articles.
Keys: RCTs = Randomised controlled trials, NERD = Non-erosive reflux disease, GERD = Gastroesophageal reflux disease, PPI = Proton pump inhibitor, PICO = Patients – Intervention – Comparator – Outcome

Quality control

The following quality control measures were applied during the selection process:

- The first 30% of titles and abstracts from the peer-reviewed literature were screened in duplicate by two independent researchers from Pallas. The results were compared and discussed before the remaining references were assessed by one researcher. During screening there was less than 5% discrepancy between the two researchers.
- The first 10% of the full-text articles from the peer-reviewed literature were assessed for relevancy and critically appraised in duplicate by two independent researchers from Pallas. The remaining full-text selection was done by one researcher in close collaboration with a second reviewer; any doubts were discussed in detail. In case of discrepancy or disagreements during the selection phase, a third researcher was consulted. The study was discussed until consensus was reached.

Preliminary critical appraisal

Limitations in the study design and implementation may bias the estimates of an intervention effect; the more serious the limitations the more likely it is that the quality of evidence will be downgraded. Based on the key risk of bias criteria used in the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach, a first estimation was made of the risk of bias of the articles included during the full-text selection.[22 23] In the full GRADE review, a more extensive critical appraisal will be applied; the final risk of bias and level of evidence will be based on outcome level instead of study level. The final risk of bias will depend on the outcome of interest and may vary between the outcomes.

For RCTs, the following limitations are likely to result in biased results and were initially judged in the scoping phase:

- Randomisation
- Allocation concealment
- Blinding
- Loss to follow-up
- Intention to treat
- Other limitations (e.g. non-validated method to assess the outcome)

3.1.2 Cost-effectiveness

After formulating the review question based on the agreement with the FOPH, the literature search was conducted using the databases PubMed (MEDLINE), Embase.com and NHS/EED. The search filters for cost-effectiveness and costing studies were embedded onto the search strategy of the efficacy, effectiveness and safety evidence, as discussed above. Similar to the search in efficacy, effectiveness

and safety, the original cost-effectiveness search strategy was amended three times. First, the generic drug names of the PPIs were added to the original search strategy. Second, the search strategy (with PPI drug names) was extended to the period from 2000 and 2008. Third, German, French and Dutch studies were screened next to the English studies. The full search strategies for each database are outlined in Appendix 9.2. The database output, including all indexed fields per record (e.g. title, authors, abstract), was exported to Endnote version X7.4, where the hits were de-duplicated.

For the cost-effectiveness search, the same selection procedure as for the effectiveness review is applied.

Inclusion and exclusion criteria

The list of inclusion and exclusion criteria applied during the selection process is presented in Table 2. Due to the lower number of search hits and more variation among studies, the inclusion/exclusion criteria are less stringent than those for the efficacy, effectiveness and safety systematic search. For instance, different from the efficacy, effectiveness and safety search, in the cost-effectiveness systematic review, all studies that included continuous or on-demand treatment, either as a comparator or as the intervention, were included to obtain all possibly relevant information that can be useful in modelling.

Table 2: Inclusion and exclusion criteria for cost-effectiveness systematic review

	Inclusion	Exclusion
Period publication	2000-2018	
Country of study	• All countries	
Language of the study	• English • French • German • Dutch	All other languages
Study design/type	Economic evaluations • cost-effectiveness • cost-minimisation • cost-benefit Other costing studies Resource use measurement	
Study quality		• Insufficient methodological quality (both inherent methodology as well as insufficient description of inherent methodology provided) • Small sample size (n<20; if not model-based, to be further determined during review process)
Study population	• Patients ≥18 years with NERD • Patients ≥18 years with uninvestigated GERD	• Healthy population • Patients <18 years • Population with other diagnosis than NERD/uninvestigated GERD
Study intervention	PPI continuous OR on-demand therapy (i.e. 6 months to 5 years)	
Study comparison		
Study outcomes	• See outcomes in PICO table (section 5.5) • Other possibly relevant outcomes, but not included in the PICO table (see section 4.2)	

Keys: NERD = Non-erosive reflux disease, GERD = Gastroesophageal reflux disease, PPI = Proton pump inhibitor, PICO = Patients – Intervention – Comparator – Outcome

Quality control

The following quality control measures were applied during the selection process:

- Due to the lower number of hits, all titles and abstracts were screened by two independent researchers from iMTA. The results were compared and discussed before proceeding to the full-text extraction phase. In case of discrepancy or disagreements during the selection phase, a third researcher was consulted. The study was discussed until consensus was reached.
- Due to the lower number of hits, all full-text articles that had been selected based on title-abstract screening were assessed for relevancy and critically appraised in duplicate by two independent researchers from iMTA. In case of discrepancy or disagreements during the selection

phase, a third researcher was consulted. The study was discussed until consensus was reached.

- The economic filter suggested on the CADTH website[b] for economic evaluations, cost/economic models on the Ovid Medline interface were used instead of the original economic filter for PubMed (MEDLINE) as given in Appendix 9.2, in order to check if any additional relevant studies were missed. Using the CADTH search filter did not yield any other additional relevant hits.

Preliminary critical appraisal

The methodological quality of the economic evaluations was assessed using the Drummond checklist for economic evaluations.[24 25] This checklist involves questions assessing whether a given economic evaluation study conforms to the guidelines provided on the study design, data collection and analysis & interpretation. Since the extended checklist included decision analytic model related questions, embedding questions from other checklists were deemed unnecessary (e.g. from the checklist from Philips et al. 2004[26]).

3.2 Other Sources

Meta-analyses and systematic reviews

Relevant meta-analyses and systematic reviews were selected during the screening of title and abstract phase. During the full-text screening phase, reference lists of these meta-analyses and systematic reviews were checked for possibly missed relevant individual articles. No additional articles were included by this process in the scoping phase as all articles referred to in these meta-analyses and systematic reviews were retrieved in the search. Data-extraction was only performed for individual articles, not for the meta-analyses and systematic reviews.

Cost-effectiveness sources

For the sake of informing potential future economic evaluations, the following studies that were beyond the scope of the inclusion criteria were also included:

- Economic evaluation studies that were comparing specific on-demand PPI treatments with each other (hence no continuous PPI treatment as a comparator).

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[b] https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#health

- Economic evaluation studies that were comparing different specific PPI treatment strategies, where on-demand treatment was a phase of the treatment strategy (e.g. on-demand strategy is initiated only if the patient responds to the initial empirical continuous PPI treatment that is set at 4 to 8 weeks).

Other HTA Domains

For the organisational aspects, the studies listed under the MESH subheadings of "proton pump inhibitors/organisation and administration" or "proton pump inhibitors/supply and distribution" on the PubMed (MEDLINE) website were screened.

For the ethical aspects, following the recommendations in the HTA Core Model Version 3.0[27], modified search filters from Droste et al. 2010[28] were embedded to the clinical search strings explained in 3.1.1. The search filter for ethical issues is provided in Appendix 9.2.

For legal aspects, the Swiss legislative database was searched for any GERD or PPI related federal, national or European level legislations[c].

For the social aspects, an additional search was not conducted, since most of the search terms (or their alternatives) suggested in the HTA Core Model Version 3.0[27] were already included in the search filter for economic or ethical issues (such as "quality of life", "patient-choice" or "patient-decision-making").

Additionally, the clinical guidelines and technology assessments from the major national health technology assessment websites were searched (i.e. NICE[d] from the UK, IQWIG[e] from Germany, HAS[f] from France, ZiN[g] from the Netherlands, CADTH[h] from Canada and PBAC[i] from Australia). This search aimed to check if the published guidelines have included possibly missed relevant evidence on the efficacy, safety, economical, organisational and ethical aspects on the PPI therapy for GERD patients. The initial search yielded the NICE clinical guideline on GERD and two reports on the CADTH webpage. No missed studies/articles were identified in these guidelines/reviews.

[c] https://www.admin.ch/opc/search/search.php?lang=en
[d] www.nice.org.uk (https://www.nice.org.uk/guidance/cg184
[e] https://www.iqwig.de/
[f] https://www.has-sante.fr/
[g] https://www.zorginstituutnederland.nl/
[h] www.cadth.ca/ (1. https://bit.ly/2pQyyZ5 2. https://bit.ly/2A6JSWX)
[i] www.pbs.gov.au/

3.3 PRISMA Flow Diagram

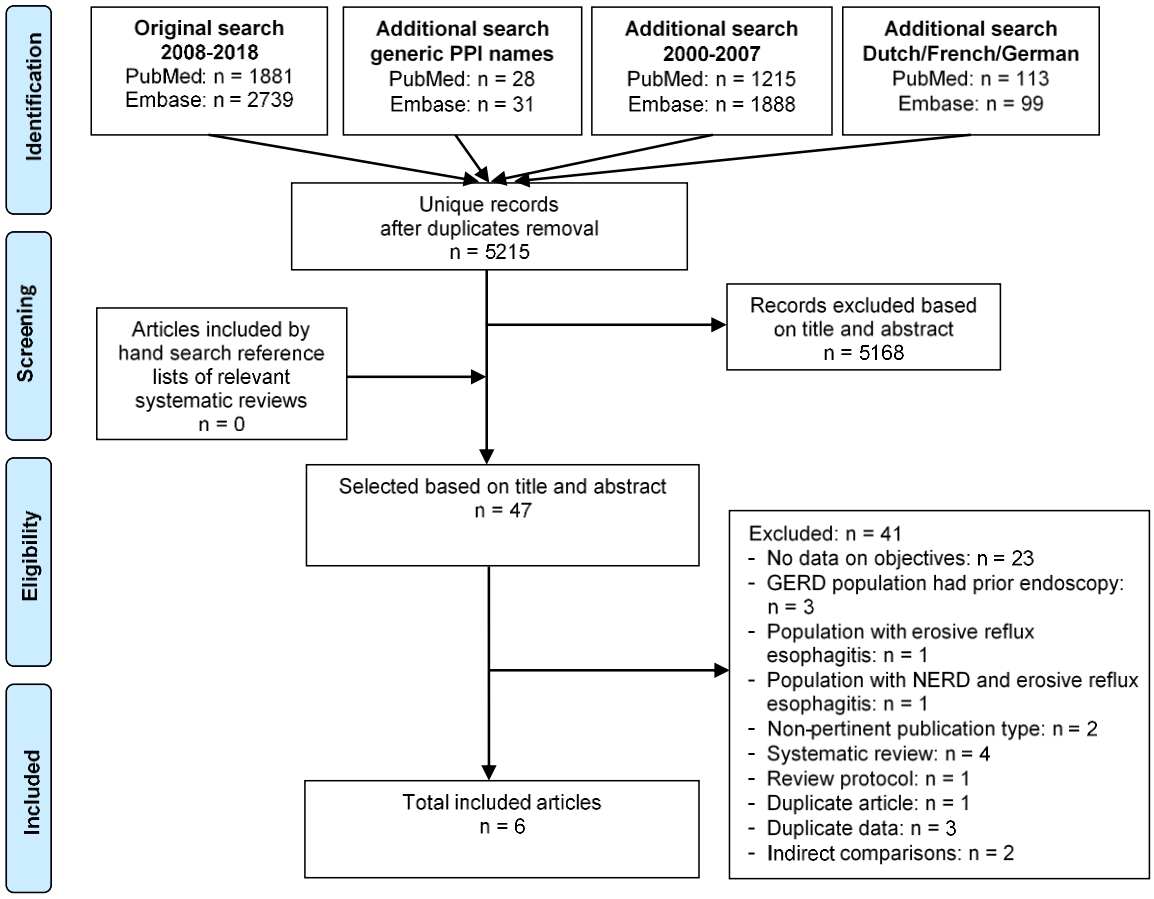
3.3.1 Efficacy, effectiveness and safety systematic review

Based on the four searches for the efficacy, effectiveness and safety review, in total 5215 unique records were identified in PubMed (MEDLINE) and Embase.com (Figure 1). Of those, 5168 records were excluded based on their title and/or abstract. Forty-seven articles were screened in full-text and six articles were included after applying the inclusion and exclusion criteria. The main reasons for exclusion were no data on objectives (n=23), no population of interest (n=5; i.e. GERD population who had a prior endoscopy (n=3), population with erosive reflux esophagitis (n=1) and population with NERD and erosive reflux esophagitis (n=1)), duplicate data (n=3), and systematic review (n=4). Two studies were excluded for the reason indirect comparisons.[16] [29] In these studies, continuous therapy was compared with on-demand therapy with a different PPI and/or different dosage of the PPI (the study characteristics are enclosed in Appendix 9.3).

3.3.2 Cost-effectiveness systematic review

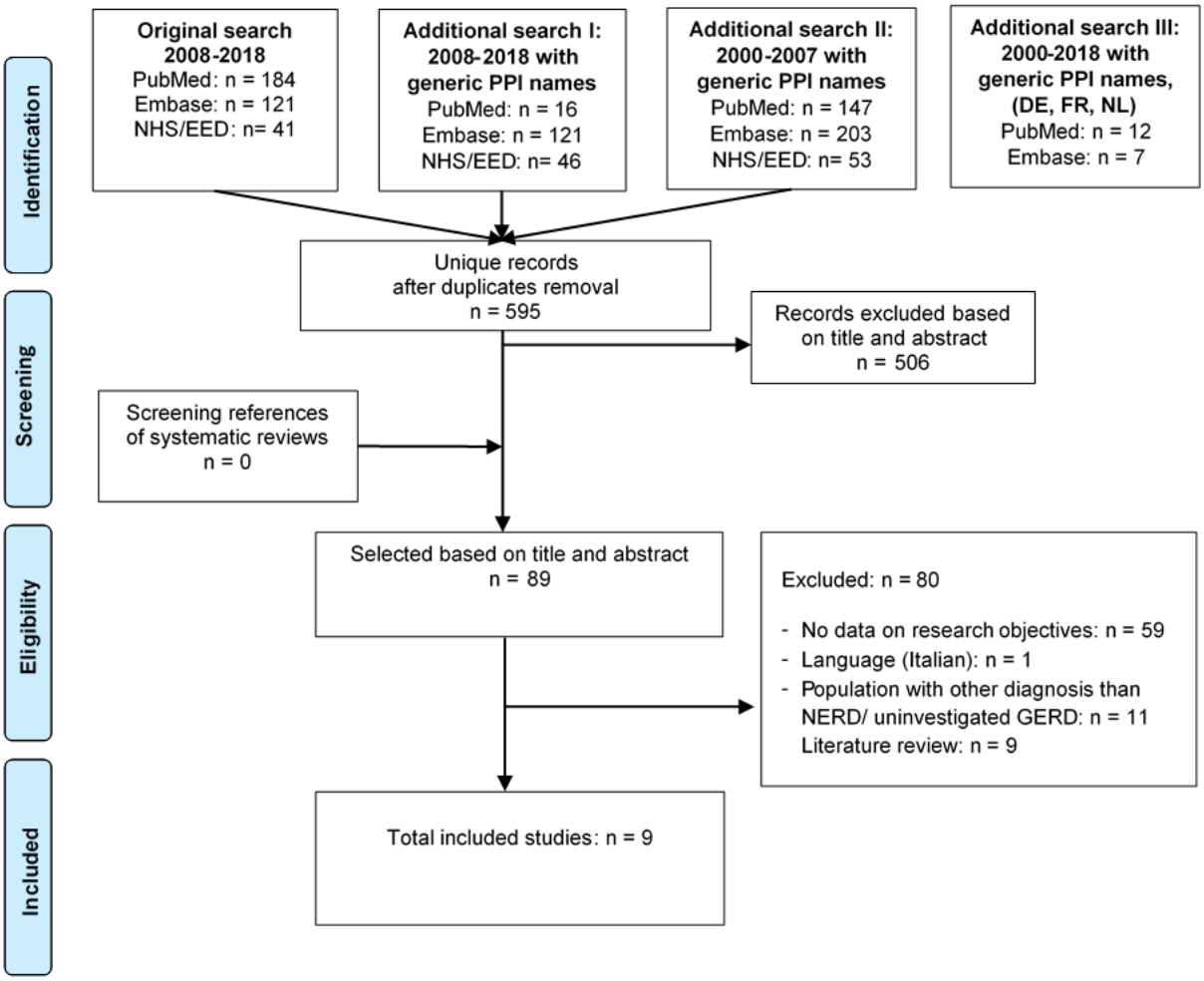
As can be seen in Figure 2, the search strategies used in the cost-effectiveness systematic review created 595 records (excluding duplicates). Of those, 506 were excluded based on their title and/or abstract. Following this, the remaining 89 records was screened in full-text to identify the relevant studies. The inclusion/exclusion criteria were applied to the screened full-text articles, which finally resulted in the selection of 9 studies. These studies were proceeded to the data extraction phase. The main reasons for excluding studies in the full-text screening phase were including no data on research objectives ((n=59) e.g. no economic study or irrelevant intervention & comparators), not original research but review of the literature (n=9), and having a different study population (n=11). One article is in Italian language and was therefore excluded.

Figure 1. PRISMA flowchart efficacy, effectiveness and safety systematic review



Keys: PPI = Proton pump inhibitors, GERD = Gastroesophageal reflux disease, NERD = Non-erosive reflux disease

Figure 2. PRISMA flowchart cost-effectiveness systematic review



Keys: PPI = Proton pump inhibitors, GERD = Gastroesophageal reflux disease, NERD = Non-erosive reflux disease

Preliminary critical appraisal of the retrieved economic evaluations

In an attempt to provide insight in the quality of the studies at a glance, the studies were assessed on their reported information. The well-established guidelines on the evaluation of economic evaluations by Drummond and Jefferson (1996)[24] were used in conjunction with the more recent checklist for critical assessment of economic evaluation from *Methods for the Economic Evaluation of Health Care Programmes* (Drummond et al., 2005)[25]. The guidelines from 1996 contained a clear and well-structured overview of the crucial elements that every full economic evaluation should provide. In 2005, the checklist was extended to provide additional guidance on the usefulness of the evaluations. Hence, the focus of the checklist is on the methodology employed, which enables the reader to make a preliminary judgement on the validity of the stated results. An alternative to the Drummond checklist(s) is the CHEERS checklist that was developed by the ISPOR task force and published in 2013. The CHEERS checklist

aimed to consolidate guidelines to optimise reporting and to provide a user-friendly manual to the assessors. The CHEERS checklist provides a practical guide to assess submitted economic evaluations of health interventions regarding the reporting of crucial elements. The CHEERS list overlaps with the lists of Drummond et al. (1996, 2005), however, Drummond's lists are more exhaustive and explicitly encourages the reviewer to critically assess the reported data (e.g. in Drummond's list there are questions such as: "*is the methodology coherent with the outlined aim?*"). Therefore, we continued with the well-established Drummond checklists, merging criteria whenever there was an overlap.

4. Synthesis of Evidence Base

4.1 Evidence Base Pertaining to Efficacy, Effectiveness and Safety

Study characteristics

In total six articles[9 30-34], reporting data of five studies, were included in the efficacy, effectiveness and safety systematic review. Hansen et al. reported the outcomes of their study in two separate articles, one focusing on the efficacy and safety aspects[33] and the second article on health-related quality of life.[9] All studies were open-label RCTs, providing data on the efficacy and safety outcomes. No non-randomised studies (i.e. non-randomised controlled trials, cohort studies or case-control studies) were identified on the effectiveness and safety of continuous versus on-demand PPI long-term therapy in adult patients with NERD or uninvestigated GERD.

An overview of the study characteristics is included in Table 3. The five studies were conducted in Canada, Japan, Norway, Switzerland and one multi-country study in Austria, France, Germany, South Africa, and Spain. Two studies investigated a NERD population and three studies patients with endoscopically uninvestigated GERD. Three different PPIs were studied to compare the efficacy and safety of continuous versus on-demand PPI long-term therapy (esomeprazole 20 mg, omeprazole 20 mg, rabeprazole 20 mg; all reflect the minimal efficacious dose); all with a treatment duration of six months. The total sample size ranged from 35 to 1904 patients. Nagahara et al., 2014 studied patients with NERD and reflux esophagitis, only part of the results was stratified for NERD patients, resulting in a small sample size of 35 patients.[32] The preliminary risk of bias was assessed for the studies: three studies had a low risk of bias, one a moderate and one study a high risk of bias. In the full GRADE review the final risk of bias and level of evidence will be based on outcome level instead of study level. The final risk of bias will depend on the outcome of interest and may vary between the outcomes.

Table 3: Study characteristics of the studies included in the efficacy, effectiveness and safety review

Reference	Country	Study design, study period	Study population	Intervention	Comparator	Sample size	Age (mean±SD in years)	Preliminary risk of bias
Bayerdörffer, 2016[30]	Austria, France, Germany, South Africa, Spain	Open-label RCT August 2001-April 2002	NERD	Continuous esomeprazole 20 mg once daily (6 months)	On-demand esomeprazole 20 mg (6 months)	- Total: 598 - Intervention: 297 - Comparator: 301	- Intervention: 47.6 ± 15.1 - Comparator: 48.2 ± 13.6	Low risk of bias
Hansen, 2005; Hansen, 2006[33 9]	Norway	Open-label RCT September 2000-November 2001	Endoscopically uninvestigated GERD	Group 1: Continuous esomeprazole 20 mg once daily (6 months)	Group 2: On-demand esomeprazole 20 mg (6 months) Group 3: Continuous ranitidine 150 mg twice-daily (6 months)	- Total: 1902 - Intervention: 658 - Comparator, group 2: 634 - Comparator, group 3: 610	- Intervention: 50.5 (SD NR) - Comparator, group 2: 51.4 (SD NR) - Comparator, group 3: 51.1 (SD NR)	Low risk of bias
Szucs, 2009[34]	Switzerland	Open-label RCT NR	Endoscopically uninvestigated GERD	Continuous esomeprazole 20 mg once daily (6 months)	On-demand esomeprazole 20 mg (6 months)	- Total: 1904 - Intervention: 913 - Comparator: 991	- Intervention: 55 ± 14.5 - Comparator: 54 ± 14.9	Low risk of bias
Nagahara, 2014[32]	Japan	Open-label RCT April 2009-April 2013	NERD	Continuous omeprazole 20 mg once daily (6 months)	On-demand omeprazole 20 mg (6 months)	- Total: 35 - Intervention: 18 - Comparator: 17	NR (total group: 56.2 ± 12.8)	High risk of bias
Morgan, 2007[31]	Canada	Open-label RCT July 2004-July 2005	Endoscopically uninvestigated GERD	Continuous rabeprazole 20 mg once daily (6 months)	On-demand rabeprazole 20 mg (6 months)	- Total: 268 - Intervention: 137 - Comparator: 131	- Intervention: 49 ± 11.0 - Comparator: 47 ± 11.0	Moderate risk of bias

Keys: RCT = Randomised controlled trial, NERD = Non-erosive reflux disease, GERD = Gastroesophageal reflux disease, NR: Not reported; SD: Standard deviation

Study outcomes

In this scoping report an overview is given which outcomes are reported in the included studies, the results of the efficacy and safety of the individual clinical trials will be extracted in the full GRADE review. An overview of the outcomes reported in the included studies is enclosed in six tables on the next pages. Separate tables are created per population type: 1. Studies in populations with endoscopically uninvestigated GERD, 2. Studies in populations with NERD, and 3. Studies in populations with endoscopically uninvestigated GERD and studies in populations with NERD merged in one table. Per population the

first table provides an overview of the preliminary predefined patient-relevant outcomes included in the PICO (see section 5), followed by a table with other not predefined outcomes reported in the included RCTs. Within the tables a stratification is made per PPI.

Endoscopically uninvestigated GERD

Population:

- Endoscopically uninvestigated GERD (4 studies)

PPIs prescribed in the included studies:

- Esomeprazole, 20 mg (3 studies)
- Rabeprazole, 20 mg (1 study)

Data reported in the included studies on the preliminary predefined patient-relevant outcomes included in the PICO (See Table 4):

- Outcome reported in 1 study:
    - PPI pill consumption per day
    - Number of endoscopic investigations per year
- Outcome reported in 2 studies:
    - HRQoL; however, not assessed with the same questionnaires
    - Symptom relief: regurgitation
- Outcome reported in 3 studies:
    - Number of therapy days per year
    - Symptom relief: heartburn
    - Safety: short-term adverse events; however 1 study with limited data
- Outcome reported in 4 studies:
    - Patient-reported therapy satisfaction; in 3 of the 4 studies the same questionnaire was used
- No data reported on the outcomes:
    - Compliance and adherence to PPI long-term therapy
    - Symptom relief: perception of flow of gastric content into oesophagus
    - Safety: long-term adverse events

Other not predefined outcomes reported in the studies (See Table 5):

- Outcome reported in 1 study:
    - Number of patients who completed the full duration of the study
    - Symptom relief: epigastric pain

    - Mean number of reflux days
    - Overall symptom relief
    - Frequency and duration of heartburn episodes
    - Duration of treatment episodes
    - Number of supplemental antacid tablets used per day
- Outcome reported in 2 studies:
    - Proportion of patients who experienced at least one relapse during the study
    - Number of patients who discontinued from treatment

NERD

Population:

- NERD (2 studies)

PPIs prescribed in the included studies:

- Esomeprazole, 20 mg (1 study)
- Omeprazole, 20 mg (1 study)

Data reported in the included studies on the preliminary predefined patient-relevant outcomes included in the PICO (See Table 6):

- Outcome reported in 1 study:
    - PPI pill consumption per day
    - Patient-reported therapy satisfaction
    - HRQoL
    - Safety: short-term adverse events; however 1 study with limited data
- No data reported on the outcomes:
    - Number of therapy days per year
    - Number of endoscopic investigations per year
    - Compliance and adherence to PPI long-term therapy
    - Symptom relief: heartburn
    - Symptom relief: regurgitation
    - Symptom relief: perception of flow of gastric content into oesophagus
    - Safety: long-term adverse events

Other not predefined outcomes reported in the studies (See Table 7):

- Outcome reported in 1 study:
    - Proportion of patients discontinuing the study as a result of unsatisfactory treatment
    - Reasons for discontinuation due to unsatisfactory treatment
- Outcome reported in 2 studies:

- Overall symptom relief; however, not assessed with the same questionnaires
- Outcome of endoscopy; development of reflux esophagitis

Endoscopically uninvestigated GERD and NERD (i.e. merged outcome tables that include studies in populations with GERD (Table 4&5) and studies in populations with NERD (Table 6&7)

Population:

- Endoscopically uninvestigated GERD (4 studies)
- NERD (2 studies)

PPIs prescribed in the included studies:

- Esomeprazole, 20 mg (4 studies)
- Omeprazole, 20 mg (1 study)
- Rabeprazole, 20 mg (1 study)

Data reported in the included studies on the preliminary predefined patient-relevant outcomes included in the PICO (See Table 8):

- Outcome reported in 1 study:
  - Number of endoscopic investigations per year
- Outcome reported in 2 studies:
  - PPI pill consumption per day
  - Symptom relief: regurgitation
- Outcome reported in 3 studies:
  - Number of therapy days per year
  - HRQoL; however, not assessed with the same questionnaires
  - Symptom relief: heartburn
- Outcome reported in 4 studies:
  - Safety: short-term adverse events; however 1 study with limited data
- Outcome reported in 5 studies:
  - Patient-reported therapy satisfaction; in 3 of the 5 studies the same questionnaire was used
- No data reported on the outcomes:
  - Compliance and adherence to PPI long-term therapy
  - Symptom relief: perception of flow of gastric content into oesophagus
  - Safety: long-term adverse events

Other not predefined outcomes reported in the studies (See Table 9):

- Outcome reported in 1 study:
    - Number of patients who completed the full duration of the study
    - Proportion of patients discontinuing the study as a result of unsatisfactory treatment
    - Reasons for discontinuation due to unsatisfactory treatment
    - Symptom relief: epigastric pain
    - Mean number of reflux days
    - Frequency and duration of heartburn episodes
    - Duration of treatment episodes
    - Number of supplemental antacid tablets used per day
- Outcome reported in 2 studies:
    - Proportion of patients who experienced at least one relapse during the study
    - Number of patients who discontinued from treatment
    - Outcome of endoscopy; development of reflux esophagitis
- Outcome reported in 3 studies:
    - Overall symptom relief; however, not assessed with the same questionnaires

To be implemented when proceeding with a full GRADE review

Based on the draft version of this scoping report, the points below were discussed with the FOPH, iMTA and Pallas; these aspects will be implemented when proceeding with a full GRADE review:

- Population: Whether to merge or stratify the population of interest in uninvestigated GERD and NERD.

  GERD describes a spectrum of different reflux diseases, including NERD, erosive reflux disease and other complicated forms. In the absence of an endoscopic examination, it is not possible to confirm the existence of an erosion. Therefore, a GERD population without endoscopy, besides NERD patients, will possibly include some patients with oesophageal mucosal erosions/breaks, as well. In the clinical practice, typically, GERD is diagnosed not by an endoscopy but by an evaluation of clinical symptoms and the response of those symptoms to acid suppression therapy. Endoscopy is often applied when the symptoms reoccur or become worse, and it is expected that the largest part of the uninvestigated GERD population with controlled symptoms is comprised of NERD patients. Therefore, it is decided to merge the data of both populations in the GRADE review. Merging the data on a population level will enlarge the feasibility of summarising the efficacy and safety data, as more data is available per outcome. In addition, where possible, sensitivity analyses will be conducted for the two populations separately.
- Intervention: Whether to merge or stratify the PPIs investigated in the studies.

Three different PPIs were studied in the selected RCTs to compare the efficacy and safety of continuous versus on-demand PPI long-term therapy (esomeprazole 20 mg, omeprazole 20 mg, rabeprazole 20 mg). There is no significant difference in the effectiveness of different PPIs at equivalent doses.[35] Therefore, it is possible to merge the data on an intervention level in the full GRADE review.

- Outcomes: Choose and define the patient-relevant outcomes to be included in the full GRADE review.

  The predefined outcomes in this scoping report (see section 5) will all be included in the GRADE review. The available data on these outcomes will be extracted and further summarised where possible. It will be reported for which outcomes no results were found in the included RCTs.

Table 4: Predefined outcomes included in the preliminary PICO in populations with endoscopically uninvestigated GERD

Reference	1a. PPI pill consumption per day	1b. Number of therapy days per year	2. Number of endoscopic investigations per year	3. Patient-reported therapy satisfaction	4. Compliance and adherence to PPI long-term therapy	5. HRQoL	6a. Symptom relief: heartburn	6b. Symptom relief: regurgitation	6c. Symptom relief: perception of flow of gastric content into oesophagus	7a. Safety: short-term adverse events	7b. Safety: long-term adverse events
Esomeprazole (20 mg)											
Hansen, 2005[33]	no	**yes (number of days with sufficient symptom control)**	no	**yes (questionnaire[a])**	no	no	**yes (% patients; severity)**	**yes (% patients)**	no	**yes**	no
Hansen, 2006[9]	no	no	no	**yes (questionnaire[a])**	no	**yes (QOLRAD[b]; OTE[c])**	no	no	no	no	no
Szucs, 2009[34]	**yes**	**yes**	**yes (during 6 months)**	**yes (questionnaire[a])**	no	no	**yes (% patients)**	**yes (% patients)**	no	**yes (limited data)**	no
Rabeprazole (20 mg)											
Morgan, 2007[31]	no	**yes (% of therapy days)**	no	**yes (questionnaire[d])**	no	**yes (PAGIQOL[e])**	**yes (% heartburn-free days)**	no	no	**yes**	no

[a] Satisfaction with treatment was assessed by patients with a 7-point Likert scale: completely satisfied, very satisfied, quite satisfied, satisfied, dissatisfied, very dissatisfied and completely dissatisfied.

[b] QOLRAD: quality of life in reflux and dyspepsia instrument. The QOLRAD questionnaire consists of 25 items grouped into 5 dimensions representing different aspects of the daily life of patients with GERD: emotional, sleep disturbance, food/drink problems, physical/social functioning, and vitality.

[c] OTE: overall treatment evaluation questionnaire. The hierarchical scale of the OTE questionnaire first asks the patient 'Since treatment started, has there been any change in your symptoms?', resulting in a response of 'better', 'about the same' or 'worse'. If the patient responds 'better' or 'worse', the patient is asked to rate the degree of change using a 7-point Likert scale to indicate how much better or worse their symptoms were. The OTE also included a question asking the patient to rate the importance of the change in their symptoms.

[d] Patients were asked to rate their overall satisfaction with their heartburn control: very dissatisfied, dissatisfied, neither dissatisfied nor satisfied, satisfied, or very satisfied.

[e] PAGIQOL: patient assessment of upper gastrointestinal disorders - quality of life questionnaire. PAGIQOL consists of 5 domain scales: daily activities (10 items), clothing (2 items), diet and food habits (7 items), relationships (3 items), and well-being and distress (8 items).

Table 5: Other not predefined outcomes reported in the included RCTs in populations with endoscopically uninvestigated GERD

Reference	Proportion of patients who experienced at least one relapse during the study	Number of patients who completed the full duration of the study	Number of patients who discontinued from treatment	Symptom relief: epigastric pain	Mean number of reflux days	Overall symptom relief	Frequency and duration of heartburn episodes	Duration of treatment episodes	Number of supplemental antacid tablets used per day
Esomeprazole (20 mg)									
Hansen, 2005[33]	**yes**	**yes**	**yes**	no	no	no	no	no	no
Hansen, 2006[9]	no	no	no	no	no	no	no	no	no
Szucs, 2009[34]	**yes**	no	no	**yes (% patients)**	**yes**	no	no	no	no
Rabeprazole (20 mg)									
Morgan, 2007[31]	no	no	**yes**	no	no	**yes (GSAS[a])**	**yes**	**yes**	**yes**

[a] GSAS: GERD symptoms assessment scale. GSAS consists of heartburn and 14 other GERD-specific symptoms.

Table 6: Predefined outcomes included in the preliminary PICO in populations with NERD

Reference	1a. PPI pill consumption per day	1b. Number of therapy days per year	2. Number of endoscopic investigations per year	3. Patient-reported therapy satisfaction	4. Compliance and adherence to PPI long-term therapy	5. HRQoL	6a. Symptom relief: heartburn	6b. Symptom relief: regurgitation	6c. Symptom relief: perception of flow of gastric content into oesophagus	7a. Safety: short-term adverse events	7b. Safety: long-term adverse events
Esomeprazole (20 mg)											
Bayerdörffer, 2016 [30]	**yes (MEMS[a])**	**yes**	no	**yes (questionnaire[b])**	no	**yes (QOLRAD[c])**	no	no	no	**yes**	no
Omeprazole (20 mg)											
Nagahara, 2014[32]	no	no	no	no	no	no	no	no	no	no	no

[a] MEMS: medical event monitoring system, Aardex, Zug, Switzerland. MEMS utilises a microelectronic recorder recessed in the cap of a drug container. At each opening and closure of the container, the date and time of day was automatically recorded.

[b] The questionnaire comprised 3 questions: “How satisfied or dissatisfied are you with the effect of the drug?”; “How satisfied or dissatisfied are you with the way of taking the drug?”; and “Overall, how satisfied or dissatisfied are you with the way of treating your heartburn and regurgitation symptoms?”. Patients were asked to give their answers as completely satisfied, quite satisfied, neither satisfied nor dissatisfied, quite dissatisfied or completely dissatisfied. For the purpose of this analysis, satisfied was defined as the sum of the upper two ratings (completely satisfied and quite satisfied).

[c] QOLRAD: quality of life in reflux and dyspepsia instrument. The QOLRAD questionnaire consists of 25 items grouped into 5 dimensions representing different aspects of the daily life of patients with GERD: emotional, sleep disturbance, food/drink problems, physical/social functioning, and vitality.

Table 7: Other not predefined outcomes reported in the included RCTs in populations with NERD

Reference	Proportion of patients discontinuing the study as a result of unsatisfactory treatment	Reasons for discontinuation due to unsatisfactory treatment	Overall symptom relief	Outcome of endoscopy
Esomeprazole (20 mg)				
Bayerdörffer, 2016[30]	**yes**	**yes**	**yes (GSRS[a])**	**yes (development of reflux esophagitis; mucosal breaks)**
Omeprazole (20 mg)				
Nagahara, 2014[32]	no	no	**yes (GOS[b])**	**yes (development of reflux esophagitis)**

[a] GSRS: gastrointestinal symptom rating scale. GSRS consists of 15 GI symptoms grouped into 5 dimensions: diarrhoea, indigestion, constipation, abdominal pain, and reflux.

[b] GOS: global overall symptom. GOS consisted of the following 8 items in this study: stomach pain, heartburn, regurgitation, postprandial fullness, vomiting, belching, early satiety, and bloating.

Table 8: Predefined outcomes included in the preliminary PICO in populations with endoscopically uninvestigated GERD and NERD (Table 4 and Table 6 merged)

Reference; population	1a. PPI pill consumption per day	1b. Number of therapy days per year	2. Number of endoscopic investigations per year	3. Patient-reported therapy satisfaction	4. Compliance and adherence to PPI long-term therapy	5. HRQoL	6a. Symptom relief: heartburn	6b. Symptom relief: regurgitation	6c. Symptom relief: perception of flow of gastric content into oesophagus	7a. Safety: short-term adverse events	7b. Safety: long-term adverse events
Esomeprazole (20 mg)											
Hansen, 2005; GERD[33]	no	**yes (number of days with sufficient symptom control)**	no	**yes (questionnaire[a])**	no	no	**yes (% patients; severity)**	**yes (% patients)**	no	**yes**	no
Hansen, 2006; GERD[9]	no	no	no	**yes (questionnaire[a])**	no	**yes (QOLRAD[b]; OTE[c])**	no	no	no	no	no
Szucs, 2009; GERD[34]	**yes**	**yes**	**yes (during 6 months)**	**yes (questionnaire[a])**	no	no	**yes (% patients)**	**yes (% patients)**	no	**yes (limited data)**	no
Bayerdörffer, 2016; NERD[30]	**yes (MEMS[d])**	**yes**	no	**yes (questionnaire[e])**	no	**yes (QOLRAD[b])**	no	no	no	**yes**	no
Omeprazole (20 mg)											
Nagahara, 2014; NERD[32]	no	no	no	no	no	no	no	no	no	no	no
Rabeprazole (20 mg)											
Morgan, 2007; GERD[31]	no	**yes (% of therapy days)**	no	**yes (questionnaire[f])**	no	**yes (PAGIQOL[g])**	**Yes (% heartburn-free days)**	no	no	**yes**	no

[a] Satisfaction with treatment was assessed by patients with a 7-point Likert scale: completely satisfied, very satisfied, quite satisfied, satisfied, dissatisfied, very dissatisfied and completely dissatisfied.

[b] QOLRAD: quality of life in reflux and dyspepsia instrument. The QOLRAD questionnaire consists of 25 items grouped into 5 dimensions representing different aspects of the daily life of patients with GERD: emotional, sleep disturbance, food/drink problems, physical/social functioning, and vitality.

[c] OTE: overall treatment evaluation questionnaire. The hierarchical scale of the OTE questionnaire first asks the patient 'Since treatment started, has there been any change in your symptoms?', resulting in a response of 'better', 'about the same' or 'worse'. If the patient responds 'better' or 'worse', the patient is asked to rate the degree of change using a 7-point Likert scale to indicate how much better or worse their symptoms were. The OTE also included a question asking the patient to rate the importance of the change in their symptoms.

[d] MEMS: medical event monitoring system, Aardex, Zug, Switzerland. MEMS utilises a microelectronic recorder recessed in the cap of a drug container. At each opening and closure of the container, the date and time of day was automatically recorded.

[e] The questionnaire comprised 3 questions: "How satisfied or dissatisfied are you with the effect of the drug?"; "How satisfied or dissatisfied are you with the way of taking the drug?"; and "Overall, how satisfied or dissatisfied are you with the way of treating your heartburn and regurgitation symptoms?". Patients were asked to give their answers as completely satisfied, quite satisfied, neither satisfied nor dissatisfied, quite dissatisfied or completely dissatisfied. For the purpose of this analysis, satisfied was defined as the sum of the upper two ratings (completely satisfied and quite satisfied).

[f] Patients were asked to rate their overall satisfaction with their heartburn control: very dissatisfied, dissatisfied, neither dissatisfied nor satisfied, satisfied, or very satisfied.

[g] PAGIQOL: patient assessment of upper gastrointestinal disorders - quality of life questionnaire. PAGIQOL consists of 5 domain scales: daily activities (10 items), clothing (2 items), diet and food habits (7 items), relationships (3 items), and well-being and distress (8 items).

Table 9: Other not predefined outcomes reported in the included RCTs in populations with endoscopically uninvestigated GERD and NERD (Table 5 & Table 7 merged)

Reference; population	Proportion of patients who experienced at least one relapse during the study	Number of patients who completed the full duration of the study	Number of patients who discontinued from treatment	Proportion of patients discontinuing the study as a result of unsatisfactory treatment	Reasons for discontinuation due to unsatisfactory treatment	Symptom relief: epigastric pain	Mean number of reflux days	Overall symptom relief	Frequency and duration of heartburn episodes	Duration of treatment episodes	Number of supplemental antacid tablets used per day	Outcome of endoscopy
Esomeprazole (20 mg)												
Hansen, 2005; GERD[33]	**yes**	**yes**	**yes**	no	no	no	no	no	no	no	no	no
Hansen, 2006; GERD[9]	no	no	no	no	no	no	no	no	no	no	no	no
Szucs, 2009; GERD[34]	**yes**	no	no	no	no	**yes (% patients)**	**yes**	no	no	no	no	no
Bayerdörffer, 2016; NERD[30]	no	no	no	**yes**	**yes**	no	no	**yes (GSRS[a])**	no	no	no	**yes (development of reflux esophagitis; mucosal breaks)**
Omeprazole (20 mg)												
Nagahara, 2014; NERD[32]	no	no	no	no	no	no	no	**yes (GOS[b])**	no	no	no	**yes (development of reflux esophagitis)**
Rabeprazole (20 mg)												
Morgan, 2007; GERD[31]	no	no	**yes**	no	no	no	no	**yes (GSAS[c])**	**yes**	**yes**	**yes**	no

[a] GSRS: gastrointestinal symptom rating scale. GSRS consists of 15 GI symptoms grouped into 5 dimensions: diarrhoea, indigestion, constipation, abdominal pain, and reflux.

[b] GOS: global overall symptom. GOS consisted of the following 8 items in this study: stomach pain, heartburn, regurgitation, postprandial fullness, vomiting, belching, early satiety, and bloating.

[c] GSAS: GERD symptoms assessment scale. GSAS consists of heartburn and 14 other GERD-specific symptoms.

Keys: NERD = Non-erosive reflux disease, GERD = Gastroesophageal reflux disease

4.2 Evidence Base Pertaining to Cost-Effectiveness Search

Study characteristics

Note that in the cost-effectiveness systematic search, less stringent inclusion criteria were applied, and any economic evaluation that included on-demand or continuous PPI long-term treatment as a comparator was considered eligible. This resulted in evaluations comparing different PPI on-demand treatments only, or studies comparing PPI on-demand treatment with PPI intermittent treatment. There are only two head-to-head continuous PPI treatment vs. on-demand PPI treatment comparisons, (Hansen et al. 2005 and Szucs et al. 2009), both of which were identified in the efficacy, effectiveness and safety search, as well.

In total nine articles were included at the end of the cost-effectiveness systematic review.[16 33 34 36-41] Of these nine economic evaluation studies, four[16 33 34 37] of them were trial-based economic evaluations and the remaining five studies[36 38-41] were model-based evaluations.

Of the trial-based economic evaluations, Hansen et al. (2005)[33] and Szucs et al. (2009)[34] provided a full economic evaluation implementing a cost-consequence analysis. According to Drummond et al. (2005), full economic evaluations must include both A) The comparison of two alternatives and B) An examination of both costs (inputs) and consequences (outputs) of the alternatives. As for the other studies, a partial economic evaluation was implemented, either in form of a cost minimisation analysis (Meineche-Schmidt et al., 2004[37]) or by providing an efficacy evaluation in combination with a brief cost analysis of the drug costs (Tsai et al., 2004)[16]. All of the trial-based studies employed a society perspective from their respective countries: Norway, Denmark, Switzerland and the UK, except Tsai et al. (2004)[16] whose economic evaluation only covered the drug costs for the study time of six months.

An overview of trial-based economic evaluations is given in Table 10. Three of these trial-based evaluations were focusing on endoscopically uninvestigated GERD patients[33 34 37] and only one study, Tsai et al. 2004 was focusing on the NERD population.[16] All these four studies were European studies (Norway, Denmark, Switzerland and the UK) and all of them were sponsored by pharmaceutical companies to some extent. All four studies were either open-label or single-blind randomised controlled trials with a follow-up period of six months. Each of them compared on-demand treatment with esomeprazole 20 mg with a variety of continuous and intermittent treatment strategies, sometimes with different drugs or dosages. For instance in Hansen et al. 2005 one of the comparators was continuous treatment with ranitidine (an H_2RA) 150 mg, twice daily.[33] In Tsai et al. 2004[16], the comparator was continuous treatment with lansoprazole 15 mg and in Maineche-Schmidt et al. 2004[37], the comparators were different lengths of intermittent treatment strategies with 40 mg esomeprazole, initiated upon symptom recurrence.

An overview of the model-based economic evaluations is given in Table 11. Two of these model-based evaluations focused on endoscopically uninvestigated GERD patients[36 40] and the remaining three studies focused on the NERD population.[38 39 41] The most recent model-based study was from 2005. The country/jurisdiction of one study was not mentioned and the remaining four studies were European studies (one Italy and three UK) and all of them were sponsored by pharmaceutical companies to some extent. All studies but Gerson et al. 2000 and Hughes et al. 2005a implemented a UK NHS perspective.[36 38] Most of the model-based evaluation studies were having a relatively short (less than or equal to one year) time horizon, except for the Gerson et al. 2000 study, which has a life-time horizon.[36] All models were decision tree/Markov models. The model-based evaluation studies that focused on NERD population were comparing on demand esomeprazole 20 mg treatment either with on-demand treatment strategies using other PPI agents[38 39] or with continuous/intermittent treatment strategies of omeprazole.[41]

The studies that focused on an endoscopically uninvestigated GERD population had more elaborate model structures.[36 40] These models included events like endoscopy, stepping up/down, symptom contingent discontinuation or surgery events. In both studies, on-demand treatment strategy is a part of the modelled treatment trajectory, and started based on the modelled patient's symptom prognosis. Note that in the Gerson et al. 2000 article, the treatment that was defined as on-demand was actually an intermittent therapy, since a patient who experienced a symptom recurrence started a treatment course of eighth weeks. This is in contrast with the definition of on-demand treatment, in which the patient can stop receiving PPI treatment at any time.[36]

Table 10: Study characteristics of the trial-based economic evaluation studies

References	Country	1. Study design 2. Study period 3. Type of evaluation	Study population	Intervention	Comparator	Outcome measure	Results
Hansen (2005)[33]	NO	1. Open- label RCT 2. 26 weeks 3. Cost consequence analysis	Endoscopically uninvestigated GERD	Group 1: Esomeprazole 20mg, on demand	Group 2: Continuous esomeprazole 20 mg once daily Group 3: Continuous ranitidine 150 mg twice-daily (6 months)	▪ Direct medical costs (physician contacts and visits, tests, procedures, medication) ▪ Direct non-medical costs (transportation) ▪ Indirect costs (loss of leisure time due to healthcare visits, loss of production due to GERD related absence from work) ▪ Treatment satisfaction ▪ Relapses (time to first relapse, number of relapses) ▪ QoL (from a different study)	Total direct medical costs: €171.9 for on-demand esomeprazole €221.6 for ranitidine €248.8 for continuous esomeprazole Total costs: €221.5 for on-demand esomeprazole €286.5 for continuous esomeprazole treatment €295.8 for ranitidine
Meineche-Schmidt (2004)[37]	DK	1. Open- label RCT 2. 6 months 3. Cost minimisation	Endoscopically uninvestigated GERD	Group 1: Esomeprazole 20mg, on demand	Group 2: Intermittent treatment, 4 weeks long 40 mg Esomeprazole course on symptom recurrence Group 3: Intermittent treatment, 2 weeks long 40 mg esomeprazole course on symptom recurrence	▪ Direct medical costs (physician contacts, tests and procedures, study medication: GERD medication, prescribed GERD medication; hospitalisation) ▪ Direct non-medical costs (transportation costs) ▪ Indirect costs (travel & visiting time costs, cost for workdays lost), ▪ Relapses (time to first relapse, number of relapses) ▪ Patient satisfaction with the treatment	Mean direct medical costs: €182 for on-demand € 221 for 2 weeks of intermittent treatment €195 for 4 weeks of intermittent treatment Mean total costs: €211 for on-demand €344 for 2 weeks of intermittent treatment €300 for 4 weeks of intermittent treatment Average number of relapses: 0.13 in the on-demand arm 2,82 in the 2-week intermittent arm 2.08 in the 4-week intermittent arm
Szucs (2009)[34]	CH	1. Open-label RCT 2. 6 months 3. Cost consequence analysis	Endoscopically uninvestigated GERD	Esomeprazole 20mg, on demand	Continuous esomeprazole 20 mg once daily	▪ Direct medical costs (study medication, other GERD-related prescribed medication, GERD-related OTC medication, unscheduled health-care contacts, GERD-related tests and procedures and hospitalisations) ▪ Direct non-medical costs (transportation) ▪ Indirect costs (productivity losses due to absence from work because of GERD, early retirement due to GERD) ▪ Treatment satisfaction ▪ Disease symptoms ▪ Time to first relapse	Incremental direct medical treatment costs of on-demand vs. continuous: CHF 88.72 (in favour of on-demand) Direct nonmedical costs and indirect costs are similar between treatment arms. GERD symptoms between on-demand and continuous are similar, continuous treatment ended up with slightly better symptoms.

References	Country	1. Study design 2. Study period 3. Type of evaluation	Study population	Intervention	Comparator	Outcome measure	Results
Tsai (2004)[16]	UK	1. Single-blind RCT 2. 6 months 3. Cost consequence analysis	NERD	Esomeprazole 20mg, on demand	Continuous lansoprazole 15 mg (6 months)	▪ Study medication usage ▪ Willingness to continue ▪ Treatment satisfaction	Mean cost per successful patient[j] was £37.85 for esomeprazole on-demand compared with £64.71 for lansoprazole continuous therapy (based on actual usage: 0.8 capsules per day). Discontinuation of continuous lansoprazole was higher than esomeprazole on-demand (7% vs. 2%; P = 0.0028). After treatment for 1 month significantly more patients receiving esomeprazole 20 mg on-demand were 'satisfied' (defined as scores of 1–4) with their treatment than those receiving continuous lansoprazole 15 mg daily (93.2% vs. 87.8%; P = 0.02; estimate of difference 5.5, 95% CI: 0.88–10.1).

Keys: QALYs = Quality-adjusted life years, RCT = Randomised controlled trial, GERD = Gastroesophageal reflux disease, HRQoL = Health-related quality of Life, OTC = Over the counter, UK = United Kingdom, NO = Norway, DK = Denmark, CH = Switzerland

[j] Successful patient is defined as a patient that continued treatment until the end of the study period.

Table 11: Study characteristics of the model-based economic evaluation studies

References	Country	1. Study design 2. Study period	Study population	Model used	Intervention	Comparator	Outcome measure	Results
Gerson (2000)[36]	US	1. CE analysis 2. Starting at age 40 until death of patient	Endoscopically uninvestigated GERD	Decision tree model	Group 1: PPI-on-demand therapy (omeprazole 20mg): 8 week of treatment for symptomatic recurrence, with no more than three courses per year	Group 2: H2RA therapy, with endoscopy performed if no response to H2RAs (generic ranitidine 150mg) Group 3: Step up (H2RA-PPI) Arm: H2RA followed by PPI therapy in the case of symptomatic failure Group 4: Step down arm: PPI therapy followed by H2RA if symptomatic response to PPI, and antacid therapy if response to H2RA therapy Group 5: Lifestyle therapy, including antacids Group 6: PPI-continuous therapy	▪ Total costs ▪ QALYs ▪ ICER	On-demand therapy cost-effectiveness ratio compared to lifestyle therapy: $20,934 per QALY for patients with moderate to severe GERD symptoms $37,923 for patients with mild GERD symptoms
Hughes[a] (2005)[38]	IT	1. CE analysis 2. 12 months	NERD	Decision tree model	Group 1: Esomeprazole 20mg, on demand	Group 2: On-demand use of lansoprazole 15 mg Group 3: On-demand use of pantoprazole 20 mg Group 4: On-demand use of rabeprazole 10 mg Group 5: On-demand use of omeprazole 10 mg Group 6: On-demand use of omeprazole 20 mg	▪ Direct medical costs ▪ Indirect medical costs ▪ Health state utilities	The lowest median cost strategy: On-demand rabeprazole €181 healthcare related costs €295 societal costs The highest median cost strategy: On-demand omeprazole 20mg €405 healthcare related costs €528 societal costs
Hughes[b] (2005)[39]	UK	1. CE analysis 2. 1 year horizon	NERD	Decision tree model	Group 1: Esomeprazole 20mg, on demand	Group 2: On-demand use of pantoprazole 20 mg Group 3: On-demand use of rabeprazole 10 mg Group 4: On-demand use of lansoprazole 15mg Group 5: On-demand use of omeprazole 10 mg Group 6: On-demand use of omeprazole 20 mg	▪ Direct medical costs ▪ Health state utilities ▪ GP consultations	Annual median costs and utilities gained with on-demand PPI therapy: €123 and 0.89 for rabeprazole 10mg €176 and 0.90 for pantoprazole 20mg €190 and 0.89 for esomeprazole 20mg €195 and 0.91 for lansoprazole 15mg €201 and 0.90 for omeprazole 20mg €210 and 0.91 for omeprazole 10mg
Wahlqvist (2002)[41]	UK	1. CE analysis 2. 6 months	NERD	Markov model	Group 1: Esomeprazole 20mg, on demand	Group 2: Intermittent 4-week acute treatment courses of omeprazole 20mg once daily; Group 3: No drug treatment followed by a continuous omeprazole treatment (20mg once daily) upon relapse	▪ Direct medical costs ▪ Relapses ▪ Symptom control	Cost reduction of 57% compared with the intermittent omeprazole strategy and 61% compared with the conventional care (continuous omeprazole) strategy.
Remak (2005)[40]	UK	1. CE analysis 2. 1 year	Endoscopically uninvestigated GERD	Decision tree model	Group 1: Rabeprazole treatment algorithm including on-demand therapy for asymptomatic patients	Group 2: omeprazole treatment algorithm Group 3: esomeprazole treatment algorithm Group 4: lansoprazole treatment algorithm Group 5: pantoprazole treatment algorithm	▪ Direct medical costs ▪ QALYs ▪ Number of symptom free days	Generic omeprazole and rabeprazole dominated (i.e. cost less and resulted in more symptom-free days and higher QALY gains) the other PPIs. Rabeprazole had a favourable cost-effectiveness ratio of £3.42 per symptom-free day and £8308/QALY gained when compared with generic omeprazole.

Keys: QALYs = Quality-adjusted life years, HRQoL = Health-related quality of Life, CE = Cost-effectiveness, GERD = Gastroesophageal reflux disease, ICER = Incremental cost-effectiveness ratio, PPI = Proton pump inhibitor, NERD: Non-erosive reflux disease, NA = Not applicable, BNF = British National Formulary, PSSRU = Personal Social Services Research Unit, NHS = National Health Service; UK = United Kingdom, CHF = Swiss Franc, US = United States, IT = Italy

Study outcomes

An overview of the outcomes reported in the included trial-based studies is enclosed in Table 12 and Table 13. The first table provides an overview of the preliminary predefined outcomes included in the PICO table (see section 5.5), followed by a table with other not predefined outcomes reported in the included RCTs.

Since the model-based economic evaluations were based on different sources of inputs (hence, not a single RCT), overview of the outcomes were not presented. The model-based economic evaluations generally reported the relevant cost and effect inputs. However, the detailed outcomes (e.g. disentangled costs or model estimations for a clinically relevant event) were only reported in Remak et al. 2005[40] (annual drug, medical visit, endoscopy costs and number of referrals, endoscopies, relapses and symptom free days in a year) and Wahlqwist et al. 2002[41] (drug, medical visit, endoscopy costs). All other studies presented aggregate level outcomes.

A jurisdiction-level budget impact analysis was only presented in the Hughes et al. 2005[39] study. No other budget impact analyses on PPIs were found.

Table 12: Assessment of the trial-based studies with regard to the predefined PICO outcomes

		TSAI (2004)[16]	MEINECHE-SCHMIDT (2004)[37]	HANSEN (2005)[33]	SZUCS(2009)[34]
1) RESOURCES USE DUE TO GERD AND PPI SIDE EFFECTS		Not available	Not available	Available	Available
2) HEALTHCARE COSTS (TOTAL AND INCREMENTAL)	a) Medication costs within 6 months, 2 years, 5 years, …, life-time (PPIs)	Medication costs within 6 months	Medication costs within 6 months	Medication costs within 6 months	Medication costs within 6 months
	b) Costs of endoscopic investigations	Not available	Not available	Available	Available
	c) Costs of adverse events/side effects	Not available	Not available	Not available	Not available
	d) Costs related to progression to erosive gastroesophageal reflux disease	Not available	Not available	Not available	Not available
	e) Costs related to hospitalisations	Not available	Available	No hospitalisations occurred	Available
3) QUALITY ADJUSTED COST COMPARISON AFTER 6 MONTHS, 2 YEARS, 5 YEARS, …, LIFE-TIME		Not available	Not available	Not available	Not available
4) NON-HEALTH RELATED CARE COSTS	a) Productivity costs	Not available	Available	Available	Available
	b) Travel costs	Not available	Available	Available	Available
	c) Caregiver costs	Not available	Available	Not available	Not available
5) INCREMENTAL COST-EFFECTIVENESS RATIO, INCREMENTAL/TOTAL COSTS, QALYS AND LYS AFTER 6 MONTHS, 2 YEARS, 5 YEARS, …, LIFE-TIME		Not available	Not available	Not available	Not available

Keys: GERD = Gastroesophageal reflux disease, NERD: Non-erosive reflux disease, PPI = Proton pump inhibitor, QALYs = Quality-adjusted life years, LYs = Life years

Table 13: Other not predefined outcomes of the trial-based studies

References	Willingness to continue (time to discontinuation in months)	Treatment satisfaction (7-point Likert scale)	Study medication usage (actual usage[a])	Time to first relapse	Average number of relapses	Symptom free	Loss of leisure time due to healthcare visits
Tsai (2004)[16]	Yes	Yes	Yes	No	No	No	No
Meineche-Schmidt (2004)[37]	No	Yes	No	Yes	Yes	Yes	No
Hansen (2005)[33]	No	Yes	No	No	No	Yes	Yes
Szucs (2009)[34]	No	Yes	No	Yes	Yes	Yes	No

[a] The actual study medication usage refers to the actual amount that the patients used rather than the prescribed one

The studies on the economic evaluation of costs and effects from the systematic literature review were assessed with the Drummond checklist below. The studies were judged on whether the criteria was fulfilled (“Yes”), not fulfilled (“No”) or it was not clearly stated (“not clear”) in the economic evaluation. Some criteria did not apply and were labelled with a “Not applicable” (“n/a”).

Among the study design items, number four (“*The rationale for choosing alternative programmes or interventions compared is stated*”) was the criterion that most of the studies failed to be considered plausible (or unclear).

Among the data collection related criteria, the following were the ones that most of the studies failed to be considered plausible (or were unclear):

- Number 16 (“*Details of currency of price adjustments for inflation or currency conversion are given.*”)
- Number 11 (“*Details of identified items omitted and/or special circumstances that made measurement difficult were described.*”)
- Number 12 (“*Capital costs and operating costs were included*.”)

Among the analysis and interpretation related points, uncertainty related items (5, 6, and 7) were the ones that most of the studies failed to be considered plausible (or were unclear).

In the model-based evaluations, the effectiveness and cost related model inputs seem not to be based on systematic literature search and the validation efforts for the model were not reported sufficiently.

Table 14: Results from the Drummond Checklist

#		Trial-based studies				Model-based studies				
		Hansen (2005)[33]	Meineche-Schmidt (2004)[37]	Szucs (2009)[34]	Tsai (2004)[16]	Gerson (2000)[36]	Hughes[a] (2005)[38]	Hughes[b] (2005)[39]	Wahlqvist (2002)[41]	Remak (2005[40])
A	**Study design**									
1	The research question is clearly stated.[a,b]	yes	yes	yes	not clear	yes	yes	yes	yes	yes
2	The economic importance of the research question is stated.[a,b]	not clear	not clear	yes	no	yes	yes	no	yes	yes
3	The viewpoint(s) of the analysis are clearly stated and justified.[a,b]	yes	yes	yes	no	not clear	not clear	yes	yes	yes
4	The rationale for choosing alternative programmes or interventions compared is stated. [a,b] (Should do nothing alternative considered?) [b]	no	no	yes	no	yes	not clear	not clear	yes*	yes
5	The alternatives being compared are clearly described.[a,b]	yes	yes	yes	yes	yes	yes	yes	yes	yes
6	The form of economic evaluation used is stated, i.e. the study examines both the costs & consequences.[a,b]	yes	yes	yes	no	yes	yes	not clear	yes	yes
7	The choice of form of economic evaluation is justified in relation to the questions addressed.[a,b]	yes	yes	yes	no	yes	yes	not clear	yes	yes
B	**Data collection**									
	Effectiveness									
1	Details of the design and results of effectiveness study are given [a,b] (if based on a single study, if done through an RCT did it reflect regular practice. [b])	yes	yes	yes	yes	yes	yes	yes	yes	yes
2	Details of the methods of synthesis or meta-analysis of estimates are given [a, b] (if based on a synthesis of a number of effectiveness studies) (Search strategies and rules for inclusion/exclusion are outlined [b]).	yes	yes	yes	yes	n/a	n/a	n/a	n/a	n/a
3	Details of potential biases are given (if based on observational data).[b]	n/a	n/a	n/a	n/a	not clear	yes	yes	not clear	not clear
	Benefit measurement & valuation									
4	The primary outcome measure(s) for the economic evaluation are clearly stated and justified.***, [a]	yes	yes	yes	yes	yes	yes	yes	yes	yes
5	Methods to value effects are stated (e.g. TTO, SG ...).[a]	yes	no	yes	yes	yes	yes	yes	no	not clear
6	Details of the subjects from whom valuations were obtained were given.[a]	yes	yes	yes	yes	not clear	yes	yes	no	no
7	Productivity changes (if included) are reported separately.[a]	yes	no	yes	no	no	yes	n/a	n/a	n/a

		Hansen (2005)[33]	Meineche-Schmidt (2004)[37]	Szucs (2009)[34]	Tsai (2004)[16]	Gerson (2000)[36]	Hughes[a] (2005)[38]	Hughes[b] (2005)[39]	Wahlqvist (2002)[41]	Remak (2005[40])
8	The relevance of productivity changes to the study question is discussed.[a]	yes	no	yes	no	no	no	n/a	n/a	yes
	Costing and valuation									
9	Sources of resource utilisation were described and justified.[b]	yes	yes	yes	no	yes	yes	yes	not clear	yes
10	Details of identified items omitted and/or special circumstances that made measurement difficult were described.[b]	yes	yes	no	no	no	no	No	no	n/a
11	Capital costs and operating costs were included.[b]	yes	yes	no	no	yes	no	No	no	no
12	Quantities of resource use are reported separately from their unit costs.[a]	no	yes	yes	not clear	no	yes	yes	no	yes
13	Methods for the estimation of quantities and unit costs are described.[a]	yes	yes	yes	not clear	yes	yes	yes	yes	not clear
14	Currency and price data are recorded.[a]	yes	yes	yes	no	yes	no	yes	yes	yes
15	Details of currency of price adjustments for inflation or currency conversion are given.[a]	no*	no*	no	no	yes	no	no*	no	no
	Modelling									
16	Details of any model used are given. (e.g. decision tree, epidemiological model, …)[a]	n/a	n/a	n/a	n/a	yes	yes	yes	yes	yes
17	The choice of model used and the key parameters on which it is based are justified.[a]	n/a	n/a	n/a	n/a	not clear	not clear	not clear	yes	yes
C	**Analysis & Interpretation**									
	Adjustments for timing of costs & benefits									
1	The time horizon of costs & benefits is stated.[a,b]	yes	yes	yes	yes	yes	yes	Yes	yes	yes
2	The discount rate(s) is stated.[a,b]	n/a**	n/a**	n/a**	n/a**	yes	n/a**	n/a**	n/a**	n/a**
3	The choice of rate(s) is justified.[a,b]	n/a	n/a	n/a	n/a	not clear	n/a	n/a	n/a	n/a
4	An explanation is given if costs or benefits are not discounted.[a,b]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
5	Incremental analysis is reported (comparing relevant alternatives).[a,b]	yes	yes	yes	no	yes	yes	Yes	yes*	yes
	Allowance for uncertainty									
6	Details of statistical test and confidence intervals are given for stochastic data.[a]	no	yes	no	no	no	not clear	not clear	no	yes
7	The approach to sensitivity analysis is given.[a]	yes	no	no	no	yes	yes	Yes	yes	yes

		Hansen (2005)[33 37]	Meineche-Schmidt (2004)[37]	Szucs (2009)[34]	Tsai (2004)[16]	Gerson (2000)[36]	Hughes[a] (2005)[38]	Hughes[b] (2005)[39]	Wahlqvist (2002)[41]	Remak (2005[40])
8	The choice of variables and the ranges/distribution of values for the sensitivity analysis is justified.[b]	no	n/a	n/a	no	no	not clear	yes	no	yes
9	The ranges over which the variable are varied are stated.[b]	yes	n/a	n/a	no	yes	not clear	not clear	yes	yes
	Presentation of results									
10	Major outcomes are presented in a disaggregated as well as aggregated form.[a]	yes	yes	yes	no	yes	yes	no	yes	yes
11	The answer to the study question is given.[a]	yes	yes	yes	not clear	yes	yes	not clear	yes	yes
12	Conclusions follow from the data reported.[a]	yes	yes	yes	not clear	yes	yes	yes	yes	yes
13	Conclusions are accompanied by the appropriate caveats.[a]	yes	yes	yes	no	yes	yes	yes	yes	not clear

*Conversion rate provided; **Time of study 6 months to 1 year; ***None of the studies justified the selection of outcome measures

[a] Drummond & Jefferson (1996)

[b] Drummond et al. (2005)

General conclusion from the cost-effectiveness search

As can be seen from Table 12, many relevant outcomes (e.g. incremental cost-effectiveness ratio) are missing from the trial-based economic evaluations. The most recent model-based economic evaluation was from 2005, hence more recent evidence, for instance the evidence from RCTs after 2005, were not incorporated in model-based analyses. Both trial-based and model-based evaluations seem to differ substantially in terms of the quality based on the critical appraisal using Drummond's checklist (Table 14).[25]

To be implemented when proceeding with a full HTA

When it is decided to proceed with a full HTA, for the cost-effectiveness analysis of continuous versus on-demand PPI long-term therapy in adult patients with NERD or uninvestigated GERD, a number of decisions have to be made with respect to the population, intervention, outcomes, evidence synthesis and economic evaluation approaches. Based on the draft version of this scoping report, the points below were discussed with the FOPH, iMTA and Pallas; these aspects will be implemented when proceeding with a full HTA:

- Population: Whether to merge or stratify the population of interest in uninvestigated GERD and NERD.

  The cost-effectiveness analysis will be conducted on both merged and on separate populations (uninvestigated GERD population and NERD population).
- Intervention: Whether to merge or stratify the PPIs investigated in the studies.

  In line with the clinical-effectiveness review, in the cost-effectiveness analysis part, the effectiveness input for the investigated PPIs will be merged. However, different scenario analyses will be conducted to explore the impact of different PPI prices on the cost-effectiveness and budget impact of switching to on-demand therapy.
- Outcomes: Evidence synthesis for the cost and cost-effectiveness related outcomes.

  The cost and cost-effectiveness related outcomes (e.g. total direct medical costs under on-demand therapy) from different trial-based and the model-based economic evaluation studies will not be synthesised in a meta-analysis, since they are currency and jurisdiction dependent.
- Economic evaluation approach: A de novo model-based economic evaluation will be conducted for assessing the cost-effectiveness of long-term on-demand versus continuous PPI therapy for uninvestigated GERD and NERD populations in Switzerland. The model will focus on the Swiss context and the impact from a payer's perspective. By developing a new economic model, we will be able to synthesise all relevant clinical and economic evidence, including the more recent RCTs and most recent cost/price information. A modelling approach will provide flexibility to

analyse different ranges of outcomes and ability to analyse the impact of different types of uncertainty (parametric, structural as well as methodological) on the results. The expected time horizon is lifetime. Type of the analyses in the economic evaluation will be cost-effectiveness/cost-utility. The cost and utility impact of the side effects are expected to be included. Type of the model will be most likely a cohort-level decision tree or a Markov model, however patient-level modelling approaches can be considered contingent on the data availability. The diagnosis of an erosive disease might be potentially considered as one of the relevant endpoints that can be modelled as an absorbing state, to which the cumulative cost, life year and QALY estimates are assigned.

- In the model, clinical/economic inputs will be based on:
    - the results from the efficacy, effectiveness, safety and cost-effectiveness searches
    - other complementary search results
    - clinical expert/practitioner inputs
    - national costing guidelines/price databases
- Different from the efficacy and safety outcomes, in the economic model, the clinical inputs can be obtained from indirect treatment comparison, as well. For instance, if there are RCTs comparing long term on-demand PPI therapy with placebo and some other RCTs comparing continuous PPI therapy with placebo, evidence from these trials can be synthesised using formal indirect treatment synthesis methods.[42]
- A further protocol will be developed to conceptualise and develop the model structure and to search for model inputs.[43]
- Overall steps of the full HTA are summarised in Section 9.4.

4.3 Evidence Base Pertaining to Legal, Social and Ethical Issues

A search on the Swiss legislation database[k] (in English, French, German languages; for all legal product types; for both national and international law documents; for both in force and not in force legislations) was conducted to find any relevant legislation documents associated with on-demand PPI treatment, from 1848 until 2019. Terms such as “reflux”, “gastroesophageal” and “proton pump inhibitors”, and their French and German translations were entered. Unfortunately, the legal documents from the search did not include any information related with the on-demand PPI treatment. In the full HTA phase, this search

[k] https://www.admin.ch/opc/search/search.php?lang=en

will be re-conducted with other terms and in other databases after consultation with an HTA expert knowledgeable in Swiss law from the FOPH.

The search filter for ethical issues applied to the efficacy, effectiveness and safety search in Embase.com and PubMed (MEDLINE) yielded 282 and 256 hits, respectively. From the title-abstract screening, none of these articles seems to be exploring ethical or societal issues. Furthermore, in none of the systematic reviews (e.g. Boghossian et al. 2017[5]), ethical or societal issues were raised. In the full HTA phase, the full-texts from the literature search will be screened together with the clinical guidelines and the narrative review studies that were identified in the clinical literature search.

4.4 Evidence Base Pertaining to Organisational Issues

There are 165 studies listed under the MESH subheadings of “proton pump inhibitors/organisation and administration” or “proton pump inhibitors/supply and distribution” in PubMed (MEDLINE). In the full HTA phase, full-texts of these studies will be screened together with the national guidelines prepared by HTA agencies.

5. Central Research Question(s)

Central HTA research question

What is the efficacy, effectiveness, safety and cost-effectiveness of continuous long-term PPI treatment (i.e. 6 months to 5 years) versus on-demand long-term PPI treatment (i.e. 6 months to 5 years) in adult NERD patients and uninvestigated GERD patients?

Research question: efficacy, effectiveness and safety systematic review

What is the efficacy, effectiveness and safety of continuous PPI long-term therapy (i.e. 6 months to 5 years) with the minimal efficacious dose versus on-demand PPI long-term therapy (i.e. 6 months to 5 years) on 30-50% of the days per year, with the minimal efficacious dose, in adult patients with NERD or uninvestigated GERD, who are symptom-free after 4-8 weeks of initial acute PPI therapy?

Research question: Costs, Budget Impact and Cost-Effectiveness

For adult patients with NERD or uninvestigated GERD, who are symptom-free after 4-8 weeks of initial acute PPI therapy, is continuous PPI long-term therapy (i.e. 6 months to 5 years) with the minimal efficacious dose cost-effective compared with on-demand PPI long-term therapy (i.e. 6 months to 5 years) on 30-50% of the days per year with the minimal efficacious dose?

5.1 Patients

The population for whom PPIs are indicated consists of adult patients (i.e. ≥18 years) with NERD or with uninvestigated GERD (i.e. no prior endoscopic investigation). A prerequisite is that these patients are symptom-free after four to eight weeks of initial acute PPI therapy.

5.2 Intervention

The technology of interest for the HTA is continuous PPI long-term therapy with the minimal efficacious dose. Continuous long-term therapy is defined as daily therapy with a duration of six months to five years. The minimal efficacious dose differs for the specific PPIs.

5.3 Comparator

The technology chosen as the comparator for the HTA is on-demand PPI long-term therapy on 30-50% of the days per year with the minimal efficacious dose. With on-demand therapy, PPIs are taken only when symptoms recur and therapy is continued until the symptoms are relieved. Long-term is defined as therapy taken during a period of six months to five years. The comparison between continuous and on-demand PPI therapy should be a direct comparison. This is defined as a comparison between the two therapy approaches with identical PPI and dosage.

5.4 Outcomes

For the scoping phase, the following preliminary patient-relevant outcomes of interest were defined:

Clinical outcomes

1. PPI pill consumption per day or number of therapy days per year
2. Number of endoscopic investigations per year
3. Patient-reported therapy satisfaction
4. Compliance and adherence to PPI long-term therapy
5. Health-related quality of life (HRQoL)
6. Symptom relief:
   - Heartburn
   - Regurgitation
   - Perception of flow of gastric content into oesophagus
7. Safety: short-term and long-term adverse events (e.g. incidence of progression to erosive gastroesophageal reflux disease or pre-cancerous Barrett's oesophagus)

Cost outcomes

1. Resource use due to GERD and PPI side effects
2. Health-care costs (total and incremental)
    a. Medication costs within 6 months, 2 years, 5 years, …, life-time (PPIs)
    b. Costs of endoscopic investigations
    c. Costs of adverse events/side effects
    d. Cost related to progression to erosive gastroesophageal reflux disease
    e. Costs related to hospitalisations
3. Quality adjusted cost comparison after 6 months, 2 years, 5 years, …, life-time
4. Non-health related care costs (will be evaluated with a scenario analysis)
    a. Productivity costs
    b. Travel costs
    c. Caregiver costs
5. Incremental cost-effectiveness ratio, incremental/total costs, QALYs and LYs after 6 months, 2 years, 5 years, …, life-time

5.5 PICO

P:	1. Adult patients with NERD, who are symptom-free after 4-8 weeks of initial acute PPI therapy 2. Adult patients with uninvestigated GERD (i.e. no prior endoscopic investigation), who are symptom-free after 4-8 weeks of initial acute PPI therapy
I:	Continuous (daily) PPI long-term therapy (i.e. 6 months to 5 years) with the minimal efficacious dose
C:	On-demand PPI long-term therapy (i.e. 6 months to 5 years) on 30-50% of the days per year with the minimal efficacious dose
O (clinical)*:	1. PPI pill consumption per day or number of therapy days per year 2. Number of endoscopic investigations per year 3. Patient-reported therapy satisfaction 4. Compliance and adherence to PPI long-term therapy 5. Health-related quality of life (HRQoL)

6. Symptom relief:
   - Heartburn
   - Regurgitation
   - Perception of flow of gastric content into oesophagus
7. Safety:
   - Short-term and long-term adverse events (e.g. incidence of progression to erosive gastroesophageal reflux disease or pre-cancerous Barrett's oesophagus)

O (costs)*:

1. Resource use due to GERD and PPI side effects
2. Health-care costs (total and incremental)
   a. Medication costs within 6 months, 2 years, 5 years, …, life-time (PPIs)
   b. Costs of endoscopic investigations
   c. Costs of adverse events/side effects
   d. Cost related to progression to erosive gastroesophageal reflux disease
   e. Costs related to hospitalisations
   f. Other resource use costs (e.g. formal caregiver costs such as nurses, general practitioners, etc.)
3. Quality adjusted cost comparison after 6 months, 2 years, 5 years, …, life-time
4. Non-health related care costs (to be used only in supplementary analyses)[a]
   d. Productivity costs
   e. Travel costs
   f. Informal caregiver costs
5. Incremental cost-effectiveness ratio, incremental/total costs, QALYs and LYs after 6 months, 2 years, 5 years, …, life-time

* Preliminary outcomes of interest as agreed upon with the FOPH and applied in the scoping phase.

[a] Non-health related care costs will not be used in the model but will be collected in the data extraction sheet just to provide insight in interpreting the cost-effectiveness results of the published studies. Furthermore, these might be incorporated in supplementary analyses.

6. HTA Key Questions

The key questions were compiled from the applicable (i.e. pharmaceutical) assessment elements from the corresponding domains of the HTA Core Model 3.0.[27] During the full HTA process, these key questions aim to guide the HTA process. The selection and adaptation of the key questions has been done in agreement with the FOPH members. The identified relevant questions will be answered by systematic

literature review, cost-effectiveness/budget impact model-based analyses and clinical expert/stake-holder inputs.

6.1 Key Questions Efficacy, Effectiveness and Safety

1. Is the continuous PPI long-term therapy safe?

2. Is the on-demand PPI long-term therapy safe?

3. Are the harms related to dosage or frequency of applying continuous PPI long-term therapy?

4. Are the harms related to dosage or frequency of applying on-demand PPI long-term therapy?

5. How does continuous PPI long-term therapy compared to on-demand PPI long-term therapy affect symptoms and findings of the disease or health condition (superior, inferior or equivalent)?

6. Do continuous PPI long-term therapy and on-demand PPI long-term therapy affect progression (or recurrence) of the disease or health condition?

7. What is the effect of continuous PPI long-term therapy compared to on-demand PPI long-term therapy on generic/disease-specific health-related quality of life?

8. Were patients satisfied with continuous PPI long-term therapy or on-demand PPI long-term therapy?

9. Do continuous PPI long-term therapy and on-demand PPI long-term therapy modify the need for hospitalisation?

6.2 Key Questions Costs, Budget Impact and Cost-Effectiveness

1. What types of resources (and in what amounts) are used when delivering continuous PPI long-term therapy and on-demand PPI long-term therapy (resource-use identification)?

2. What is the likely budget impact of continuous PPI long-term therapy compared to on-demand PPI long-term therapy?

3. What are the estimated differences in costs and outcomes between continuous PPI long-term therapy and on-demand PPI long-term therapy?

4. What are the uncertainties surrounding the costs and economic evaluation(s) of continuous PPI long-term therapy and of on-demand PPI long-term therapy?

6.3 Key Questions Legal, Social and Ethical Issues

1. Are there specific legal issues associated with a potential change in reimbursement of the continuous PPI long-term therapy?

2. What are the morally relevant consequences (benefits and harms) of a potential change in reimbursement of continuous PPI long-term therapy?

6.4 Key Questions Organisational Issues

1. What organisational issues are attached to continuous PPI long-term therapy and to on-demand PPI long-term therapy?

7. Feasibility HTA

The aim of this scoping report is to determine the feasibility of conducting a Health Technology Assessment evaluation comparing efficacy, effectiveness, safety and cost-effectiveness of long-term continuous versus on-demand PPI treatment in adult NERD patients and uninvestigated GERD patients.

The evidence base for the efficacy, effectiveness and safety systematic review resulted in five randomised clinical trials for which a range of outcomes was reported in six articles.

The evidence base obtained from the cost-effectiveness search resulted in a number of economic evaluations. These are either trial-based or model-based studies. Only two studies were directly comparing on-demand PPI treatment strategy with continuous PPI treatment strategy. The identified trial-based studies do not provide sufficient evidence on the cost-effectiveness of continuous PPI treatment versus on-demand PPI treatment in the Swiss context.

Identified model-based studies are quite outdated; the most recent model-based study was dating back from 2005. Hence, in these models, evidence from the trials after 2005 were not incorporated. Generic options for PPIs were therefore not yet available to consider in the models. Considering the potential changes in the clinical practice and the poor reporting of the model details and uncertainty/budget impact analysis results, a de-novo model that incorporates the most recent effectiveness/cost and utility evidence seem to be necessary.

The current models are expected to inform during the conceptual modelling phase, concerning the model structure and modelling assumptions and placeholder model inputs. The efficacy, effectiveness

and safety search and a full GRADE assessment of the outcomes, together with other targeted searches and clinical expert inputs expect to provide sufficient evidence to build and populate a de-novo model.

The information retrieval attempts for legal, societal, ethical and organisational issues did not yield sufficient evidence for the time being. The search on these issues needs to be widened in the full HTA.

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9. Appendices

9.1 Search strategy for the efficacy, effectiveness and safety systematic review

9.1.1 Original search 2008-2018

PubMed (MEDLINE)

#1 P: NERD/GERD

non-erosive reflux disease[tiab] OR nonerosive reflux disease[tiab] OR NERD[tiab] OR gastroesophageal reflux disease[tiab] OR gastrooesophageal reflux disease[tiab] OR gastro-esophageal reflux disease[tiab] OR gastro-oesophageal reflux disease[tiab] OR GERD[tiab]

#2 I: PPI therapy

"Proton Pump Inhibitors"[Mesh] OR proton pump inhibitor*[tiab] OR PPI*[tiab]

Limits

- Publication period: 2008-2018
- Language: English only
- No animal studies:

  #3. Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh])
- No case reports and non-pertinent publication types:

  #4. case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt]

Number of hits PubMed (MEDLINE) ((#1 AND #2) NOT (#3 OR #4)):

- 1881 hits (11-07-2018)

Embase.com

#1 P: NERD/GERD

'non erosive reflux disease':ab,ti OR 'nonerosive reflux disease':ab,ti OR nerd:ab,ti OR 'gastroesophageal reflux disease':ab,ti OR 'gastrooesophageal reflux disease':ab,ti OR 'gastro-esophageal reflux disease':ab,ti OR 'gastro-oesophageal reflux disease':ab,ti OR gerd:ab,ti

#2 I: PPI therapy

'proton pump inhibitor'/exp OR 'proton pump inhibitor*':ab,ti OR ppi*:ab,ti

Limits

- Publication period: 2008-2018
- Language: English only
- No case reports and non-pertinent publication types:

  #3. [article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [erratum]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim

Number of hits Embase.com ((#1 AND #2) NOT (#3)):

- 2739 hits (11-07-2018)

9.1.2 Additional search generic PPI brand names

PubMed (MEDLINE)

#1 P: NERD/GERD

non-erosive reflux disease[tiab] OR nonerosive reflux disease[tiab] OR NERD[tiab] OR gastroesophageal reflux disease[tiab] OR gastrooesophageal reflux disease[tiab] OR gastro-esophageal reflux disease[tiab] OR gastro-oesophageal reflux disease[tiab] OR GERD[tiab]

#2 I: generic PPI drug names

omeprazole[tiab] OR lansoprazole[tiab] OR esomeprazole[tiab] OR pantoprazole[tiab] OR rabeprazole[tiab] OR dexlansoprazole[tiab] OR ilaprazole[tiab]

Limits

- Publication period: 2008-2018
- Language: English only
- No animal studies:

  #3. Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh])
- No case reports and non-pertinent publication types:

#4. case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt]

Number of hits PubMed (MEDLINE) ((#1 AND #2) NOT (#3 OR #4)):

- 553 hits (21-08-2018)
- Unduplicated with original search: 28 hits

Embase.com

#1 P: NERD/GERD

'non erosive reflux disease':ab,ti OR 'nonerosive reflux disease':ab,ti OR nerd:ab,ti OR 'gastroesophageal reflux disease':ab,ti OR 'gastrooesophageal reflux disease':ab,ti OR 'gastro-esophageal reflux disease':ab,ti OR 'gastro-oesophageal reflux disease':ab,ti OR gerd:ab,ti

#2 I: generic PPI drug names

omeprazole:ab,ti OR lansoprazole:ab,ti OR esomeprazole:ab,ti OR pantoprazole:ab,ti OR rabeprazole:ab,ti OR dexlansoprazole:ab,ti OR ilaprazole:ab,ti

Limits

- Publication period: 2008-2018
- Language: English only
- No case reports and non-pertinent publication types:
  #3. [article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [erratum]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim

Number of hits Embase.com ((#1 AND #2) NOT (#3)):

- 622 hits (21-08-2018)
- Unduplicated with original search: 31 hits

9.1.3 Additional search 2000-2007

PubMed (MEDLINE)

#1 P: NERD/GERD

non-erosive reflux disease[tiab] OR nonerosive reflux disease[tiab] OR NERD[tiab] OR gastroesophageal reflux disease[tiab] OR gastrooesophageal reflux disease[tiab] OR gastro-esophageal reflux disease[tiab] OR gastro-oesophageal reflux disease[tiab] OR GERD[tiab]

#2 I: PPI therapy

"Proton Pump Inhibitors"[Mesh] OR proton pump inhibitor*[tiab] OR PPI*[tiab] OR omeprazole[tiab] OR lansoprazole[tiab] OR esomeprazole[tiab] OR pantoprazole[tiab] OR rabeprazole[tiab] OR dexlansoprazole[tiab] OR ilaprazole[tiab]

Limits

- Publication period: 2000-2007
- Language: English only
- No animal studies:
  #3. Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh])
- No case reports and non-pertinent publication types:
  #4. case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt]

Number of hits PubMed (MEDLINE) ((#1 AND #2) NOT (#3 OR #4)):

- 1215 hits (27-08-2018)

Embase.com

#1 P: NERD/GERD

'non erosive reflux disease':ab,ti OR 'nonerosive reflux disease':ab,ti OR nerd:ab,ti OR 'gastroesophageal reflux disease':ab,ti OR 'gastrooesophageal reflux disease':ab,ti OR 'gastro-esophageal reflux disease':ab,ti OR 'gastro-oesophageal reflux disease':ab,ti OR gerd:ab,ti

#2 I: PPI therapy

'proton pump inhibitor'/exp OR 'proton pump inhibitor*':ab,ti OR ppi*:ab,ti OR omeprazole:ab,ti OR lansoprazole:ab,ti OR esomeprazole:ab,ti OR pantoprazole:ab,ti OR rabeprazole:ab,ti OR dexlansoprazole:ab,ti OR ilaprazole:ab,ti

Limits

- Publication period: 2000-2007
- Language: English only
- No case reports and non-pertinent publication types:

  #3. [article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [erratum]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim

Number of hits Embase.com ((#1 AND #2) NOT (#3)):

- 1888 hits (27-08-2018)

9.1.4 Additional search Dutch, French, German

PubMed (MEDLINE)

#1 P: NERD/GERD

non-erosive reflux disease[tiab] OR nonerosive reflux disease[tiab] OR NERD[tiab] OR gastroesophageal reflux disease[tiab] OR gastrooesophageal reflux disease[tiab] OR gastro-esophageal reflux disease[tiab] OR gastro-oesophageal reflux disease[tiab] OR GERD[tiab]

#2 I: PPI therapy

"Proton Pump Inhibitors"[Mesh] OR proton pump inhibitor*[tiab] OR PPI*[tiab] OR omeprazole[tiab] OR lansoprazole[tiab] OR esomeprazole[tiab] OR pantoprazole[tiab] OR rabeprazole[tiab] OR dexlansoprazole[tiab] OR ilaprazole[tiab]

Limits

- Publication period: 2000-2018
- Language: Dutch, French, German
- No animal studies:

  #3. Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh])
- No case reports and non-pertinent publication types:

  #4. case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt]

Number of hits PubMed (MEDLINE) ((#1 AND #2) NOT (#3 OR #4)):

- 113 hits (2-10-2018)

Embase.com

#1 P: NERD/GERD

'non erosive reflux disease':ab,ti OR 'nonerosive reflux disease':ab,ti OR nerd:ab,ti OR 'gastroesophageal reflux disease':ab,ti OR 'gastrooesophageal reflux disease':ab,ti OR 'gastro-esophageal reflux disease':ab,ti OR 'gastro-oesophageal reflux disease':ab,ti OR gerd:ab,ti

#2 I: PPI therapy

'proton pump inhibitor'/exp OR 'proton pump inhibitor*':ab,ti OR ppi*:ab,ti OR omeprazole:ab,ti OR lansoprazole:ab,ti OR esomeprazole:ab,ti OR pantoprazole:ab,ti OR rabeprazole:ab,ti OR dexlansoprazole:ab,ti OR ilaprazole:ab,ti

Limits

- Publication period: 2000-2018
- Language: Dutch, French, German
- No case reports and non-pertinent publication types:
  #3. [article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [erratum]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim

Number of hits Embase.com ((#1 AND #2) NOT (#3)):

- 99 hits (2-10-2018)

9.2 Search Strategy for the cost-effectiveness systematic review

9.2.1 Original search 2008-2018

PubMed (MEDLINE)

#1 P: NERD/GERD

non-erosive reflux disease[tiab] OR nonerosive reflux disease[tiab] OR NERD[tiab] OR gastroesophageal reflux disease[tiab] OR gastrooesophageal reflux disease[tiab] OR gastro-esophageal reflux disease[tiab] OR gastro-oesophageal reflux disease[tiab] OR GERD[tiab]

#2 I: PPI therapy

"Proton Pump Inhibitors"[Mesh] OR proton pump inhibitor*[tiab] OR PPI*[tiab]

#3 Ec: Economic evaluation

(#3i OR #3ii OR #3iii OR #3iv OR #3v OR #3vi OR #3vii OR #3viii OR #3ix OR #3x OR #3xi OR #3xii OR #3xiii in [All fields])

i. economics OR “economic aspect” OR cost OR “health care cost” OR “drug cost” OR “hospital cost” OR socioeconomics OR “health economics” OR “pharmacoeconomics” OR “fee” OR “budget” OR “economic evaluation” OR “hospital finance” OR “financial management” OR “health care financing”
ii. “low cost” OR “high cost” OR “healthcare costs” OR (healthcare AND cost) OR fiscal OR funding OR financial OR finance
iii. (cost AND estimate*) OR “cost estimate” OR “cost variable” OR (unit AND cost)
iv. economic* OR pharmacoeconomic* OR price* OR pricing
v. (healthcare OR “health care”) AND (utilization OR utilisation)
vi. cost* AND (treat* OR therap*)
vii. (direct OR indirect) AND cost*
viii. “cost effectiveness analysis” OR “cost benefit analysis” OR “cost utility analysis” OR “cost minimization analysis” OR “economic evaluation”
ix. (economic OR “cost-benefit” OR “cost-effectiveness” OR “cost-utility”) AND (evaluation* OR analys* OR model* OR intervention*)
x. (“cost minimization” OR “cost minimisation”) AND (analys* OR model*)
xi. “resource use” OR “resource utilization" OR “resource utilisation”
xii. (“treatment costs” OR “costs of treatment” OR “cost of treatment” OR “costs of therapy” OR “cost of therapy” OR “cost of treating”)
xiii. economic AND (evaluation* OR model)

Limits

- Publication period: 2008-2018
- Language: English only
- No animal studies:

  #4. Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh])
- No case reports and non-pertinent publication types:

#5. case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt]

Number of hits PubMed (MEDLINE) ((#1 AND #2 AND #3) NOT (#4 OR #5)):

- 184 hits (11-07-2018)

Embase.com

#1 P: NERD/GERD

'non erosive reflux disease':ab,ti OR 'nonerosive reflux disease':ab,ti OR nerd:ab,ti OR 'gastroesophageal reflux disease':ab,ti OR 'gastrooesophageal reflux disease':ab,ti OR 'gastro-esophageal reflux disease':ab,ti OR 'gastro-oesophageal reflux disease':ab,ti OR gerd:ab,ti

#2 I: PPI therapy

'proton pump inhibitor'/exp OR 'proton pump inhibitor*':ab,ti OR ppi*:ab,ti

#3 Ec: Economic evaluation

'economics'/de OR 'economic aspect'/de OR 'cost'/de OR 'health care cost'/de OR 'drug cost'/de OR 'hospital cost'/de OR 'socioeconomics'/de OR 'health economics'/de OR 'pharmacoeconomics'/de OR 'fee'/exp OR 'budget'/exp OR 'economic evaluation'/exp OR 'hospital finance'/de OR 'financial management'/de OR 'health care financing'/de OR 'low cost' OR 'high cost' OR health*care NEXT/1 cost* OR 'health care' NEXT/1 cost* OR fiscal OR funding OR financial OR finance OR cost NEXT/1 estimate* OR 'cost variable' OR unit NEXT/1 cost* OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti OR (cost* NEAR/3 (treat* OR therap*)):ab,ti OR health*care NEXT/1 (utilisation OR utilization) OR 'health care' NEXT/1 (utilisation OR utilization) OR resource NEXT/1 (utilisation OR utilization OR use)

Limits

- Publication period: 2008-2018
- Language: English only
- No case reports and non-pertinent publication types:
  #4. [article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [erratum]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim

Number of hits Embase.com ((#1 AND #2 AND #3) NOT (#4)):

- 121 hits (11-07-2018)

University of York CRD databases (DARE, NHS/EED and HTA databases)

(reflux disease) AND (PPI* OR proton pump inhibitor*) FROM 2008 TO 2018 in Any field

Number of hits CRD databases:

- 41 hits (11-07-2018)

9.2.2 Additional search generic PPI brand names

PubMed (MEDLINE)

#1 P: NERD/GERD

non-erosive reflux disease[tiab] OR nonerosive reflux disease[tiab] OR NERD[tiab] OR gastroesophageal reflux disease[tiab] OR gastrooesophageal reflux disease[tiab] OR gastro-esophageal reflux disease[tiab] OR gastro-oesophageal reflux disease[tiab] OR GERD[tiab]

#2 I: generic PPI drug names

omeprazole[tiab] OR lansoprazole[tiab] OR esomeprazole[tiab] OR pantoprazole[tiab] OR rabeprazole[tiab] OR dexlansoprazole[tiab] OR ilaprazole[tiab]

#3 Ec: Economic evaluation

(#3i OR #3ii OR #3iii OR #3iv OR #3v OR #3vi OR #3vii OR #3viii OR #3ix OR #3x OR #3xi OR #3xii OR #3xiii in [All fields])

i. economics OR “economic aspect” OR cost OR “health care cost” OR “drug cost” OR “hospital cost” OR socioeconomics OR “health economics” OR “pharmacoeconomics” OR “fee” OR “budget” OR “economic evaluation” OR “hospital finance” OR “financial management” OR “health care financing”
ii. “low cost” OR “high cost” OR “healthcare costs” OR (healthcare AND cost) OR fiscal OR funding OR financial OR finance
iii. (cost AND estimate*) OR “cost estimate” OR “cost variable” OR (unit AND cost)
iv. economic* OR pharmacoeconomic* OR price* OR pricing
v. (healthcare OR “health care”) AND (utilization OR utilisation)
vi. cost* AND (treat* OR therap*)

vii. (direct OR indirect) AND cost*

viii. “cost-effectiveness analysis” OR “cost benefit analysis” OR “cost utility analysis” OR “cost minimization analysis” OR “economic evaluation”

ix. (economic OR “cost-benefit” OR “cost-effectiveness” OR “cost-utility”) AND (evaluation* OR analys* OR model* OR intervention*)

x. (“cost minimization” OR “cost minimisation”) AND (analys* OR model*)

xi. “resource use” OR “resource utilization" OR “resource utilisation”

xii. (“treatment costs” OR “costs of treatment” OR “cost of treatment” OR “costs of therapy” OR “cost of therapy” OR “cost of treating”)

xiii. economic AND (evaluation* OR model)

Limits

- Publication period: 2008-2018
- Language: English only
- No animal studies:
  #4. Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh])
- No case reports and non-pertinent publication types:
  #5. case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt]

Number of hits PubMed (MEDLINE) ((#1 AND #2 AND #3) NOT (#4 OR #5)):

- 35 hits (11-07-2018)
- After re-duplication from the original search: 6 hits

Embase.com

#1 P: NERD/GERD

'non erosive reflux disease':ab,ti OR 'nonerosive reflux disease':ab,ti OR nerd:ab,ti OR 'gastroesophageal reflux disease':ab,ti OR 'gastrooesophageal reflux disease':ab,ti OR 'gastro-esophageal reflux disease':ab,ti OR 'gastro-oesophageal reflux disease':ab,ti OR gerd:ab,ti

#2 I: PPI therapy

omeprazole:ab,ti OR lansoprazole:ab,ti OR esomeprazole:ab,ti OR pantoprazole:ab,ti OR rabeprazole:ab,ti OR dexlansoprazole:ab,ti OR ilaprazole:ab,ti

#3 Ec: Economic evaluation

'economics'/de OR 'economic aspect'/de OR 'cost'/de OR 'health care cost'/de OR 'drug cost'/de OR 'hospital cost'/de OR 'socioeconomics'/de OR 'health economics'/de OR 'pharmacoeconomics'/de OR 'fee'/exp OR 'budget'/exp OR 'economic evaluation'/exp OR 'hospital finance'/de OR 'financial management'/de OR 'health care financing'/de OR 'low cost' OR 'high cost' OR health*care NEXT/1 cost* OR 'health care' NEXT/1 cost* OR fiscal OR funding OR financial OR finance OR cost NEXT/1 estimate* OR 'cost variable' OR unit NEXT/1 cost* OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti OR (cost* NEAR/3 (treat* OR therap*)):ab,ti OR health*care NEXT/1 (utilisation OR utilization) OR 'health care' NEXT/1 (utilisation OR utilization) OR resource NEXT/1 (utilisation OR utilization OR use)

Limits

- Publication period: 2008-2018
- Language: English only
- No case reports and non-pertinent publication types:
  #4. [article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [erratum]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim

Number of hits Embase.com ((#1 AND #2 AND #3) NOT (#4)):

- 39 hits (11-07-2018)
- After re-duplication from the original search: 0 hits

University of York CRD databases (DARE, NHS/EED and HTA databases)

Search strings NHSEED

(reflux disease) AND (omeprazole OR lansoprazole OR esomeprazole OR pantoprazole OR rabeprazole OR dexlansoprazole OR ilaprazole) from 2008 to 2018 in any field

Number of hits CRD databases:

- 21 hits (11-07-2018)
- After re-duplication from the original search: 5 hits

9.2.3 Additional search 2000-2007

PubMed (MEDLINE)

#1 P: NERD/GERD

non-erosive reflux disease[tiab] OR nonerosive reflux disease[tiab] OR NERD[tiab] OR gastroesophageal reflux disease[tiab] OR gastrooesophageal reflux disease[tiab] OR gastro-esophageal reflux disease[tiab] OR gastro-oesophageal reflux disease[tiab] OR GERD[tiab]

#2 I: PPI therapy

"Proton Pump Inhibitors"[Mesh] OR proton pump inhibitor*[tiab] OR PPI*[tiab] OR omeprazole[tiab] OR lansoprazole[tiab] OR esomeprazole[tiab] OR pantoprazole[tiab] OR rabeprazole[tiab] OR dexlansoprazole[tiab] OR ilaprazole[tiab]

#3 Ec: Economic evaluation

(#3i OR #3ii OR #3iii OR #3iv OR #3v OR #3vi OR #3vii OR #3viii OR #3ix OR #3x OR #3xi OR #3xii OR #3xiii in [All fields])

i. economics OR “economic aspect” OR cost OR “health care cost” OR “drug cost” OR “hospital cost” OR socioeconomics OR “health economics” OR “pharmacoeconomics” OR “fee” OR “budget” OR “economic evaluation” OR “hospital finance” OR “financial management” OR “health care financing”
ii. “low cost” OR “high cost” OR “healthcare costs” OR (healthcare AND cost) OR fiscal OR funding OR financial OR finance
iii. (cost AND estimate*) OR “cost estimate” OR “cost variable” OR (unit AND cost)
iv. economic* OR pharmacoeconomic* OR price* OR pricing
v. (healthcare OR “health care”) AND (utilization OR utilisation)
vi. cost* AND (treat* OR therap*)
vii. (direct OR indirect) AND cost*
viii. “cost effectiveness analysis” OR “cost benefit analysis” OR “cost utility analysis” OR “cost minimization analysis” OR “economic evaluation”
ix. (economic OR “cost-benefit” OR “cost-effectiveness” OR “cost-utility”) AND (evaluation* OR analys* OR model* OR intervention*)
x. (“cost minimization” OR “cost minimisation”) AND (analys* OR model*)
xi. “resource use” OR “resource utilization" OR “resource utilisation”

xii. (“treatment costs” OR “costs of treatment” OR “cost of treatment” OR “costs of therapy” OR “cost of therapy” OR “cost of treating”)

xiii. economic AND (evaluation* OR model)

Limits

- Publication period: 2000-2007
- Language: English only
- No animal studies:
  #4. Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh])
- No case reports and non-pertinent publication types:
  #5. case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt]

Number of hits PubMed (MEDLINE) ((#1 AND #2 AND #3) NOT (#4 OR #5)):

- 203 hits (13-08-2018)

Embase.com

#1 P: NERD/GERD

'non erosive reflux disease':ab,ti OR 'nonerosive reflux disease':ab,ti OR nerd:ab,ti OR 'gastroesophageal reflux disease':ab,ti OR 'gastrooesophageal reflux disease':ab,ti OR 'gastro-esophageal reflux disease':ab,ti OR 'gastro-oesophageal reflux disease':ab,ti OR gerd:ab,ti

#2 I: PPI therapy

'proton pump inhibitor'/exp OR 'proton pump inhibitor*':ab,ti OR ppi*:ab,ti OR omeprazole:ab,ti OR lansoprazole:ab,ti OR esomeprazole:ab,ti OR pantoprazole:ab,ti OR rabeprazole:ab,ti OR dexlansoprazole:ab,ti OR ilaprazole:ab,ti

#3 Ec: Economic evaluation

'economics'/de OR 'economic aspect'/de OR 'cost'/de OR 'health care cost'/de OR 'drug cost'/de OR 'hospital cost'/de OR 'socioeconomics'/de OR 'health economics'/de OR 'pharmacoeconomics'/de OR 'fee'/exp OR 'budget'/exp OR 'economic evaluation'/exp OR 'hospital finance'/de OR 'financial management'/de OR 'health care financing'/de OR 'low cost' OR 'high cost' OR health*care NEXT/1 cost* OR 'health care' NEXT/1 cost* OR fiscal OR funding OR financial OR finance OR cost NEXT/1 estimate*

OR 'cost variable' OR unit NEXT/1 cost* OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti OR (cost* NEAR/3 (treat* OR therap*)):ab,ti OR health*care NEXT/1 (utilisation OR utilization) OR 'health care' NEXT/1 (utilisation OR utilization) OR resource NEXT/1 (utilisation OR utilization OR use)

Limits

- Publication period: 2000-2007
- Language: English only
- No case reports and non-pertinent publication types:
  #4. [article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [erratum]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim

Number of hits Embase.com ((#1 AND #2 AND #3) NOT (#4)):

- 147 hits (13-08-2018)

University of York CRD databases (DARE, NHS/EED and HTA databases)

(reflux disease) AND (PPI* OR proton pump inhibitor* OR omeprazole OR lansoprazole OR esomeprazole OR pantoprazole OR rabeprazole OR dexlansoprazole OR ilaprazole) FROM 2000 TO 2007 in Any field

Number of hits CRD databases:

- 53 hits (13-08-2018)

9.2.4 Additional search Dutch, French, German

PubMed (MEDLINE)

#1 P: NERD/GERD
non-erosive reflux disease[tiab] OR nonerosive reflux disease[tiab] OR NERD[tiab] OR gastroesophageal reflux disease[tiab] OR gastrooesophageal reflux disease[tiab] OR gastro-esophageal reflux disease[tiab] OR gastro-oesophageal reflux disease[tiab] OR GERD[tiab]

#2 I: PPI therapy
"Proton Pump Inhibitors"[Mesh] OR proton pump inhibitor*[tiab] OR PPI*[tiab] OR omeprazole[tiab] OR lansoprazole[tiab] OR esomeprazole[tiab] OR pantoprazole[tiab] OR rabeprazole[tiab] OR dexlansoprazole[tiab] OR ilaprazole[tiab]

#3 Ec: Economic evaluation

(#3i OR #3ii OR #3iii OR #3iv OR #3v OR #3vi OR #3vii OR #3viii OR #3ix OR #3x OR #3xi OR #3xii OR #3xiii in [All fields])

i. economics OR “economic aspect” OR cost OR “health care cost” OR “drug cost” OR “hospital cost” OR socioeconomics OR “health economics” OR “pharmacoeconomics” OR “fee” OR “budget” OR “economic evaluation” OR “hospital finance” OR “financial management” OR “health care financing”
ii. “low cost” OR “high cost” OR “healthcare costs” OR (healthcare AND cost) OR fiscal OR funding OR financial OR finance
iii. (cost AND estimate*) OR “cost estimate” OR “cost variable” OR (unit AND cost)
iv. economic* OR pharmacoeconomic* OR price* OR pricing
v. (healthcare OR “health care”) AND (utilization OR utilisation)
vi. cost* AND (treat* OR therap*)
vii. (direct OR indirect) AND cost*
viii. “cost effectiveness analysis” OR “cost benefit analysis” OR “cost utility analysis” OR “cost minimization analysis” OR “economic evaluation”
ix. (economic OR “cost-benefit” OR “cost-effectiveness” OR “cost-utility”) AND (evaluation* OR analys* OR model* OR intervention*)
x. (“cost minimization” OR “cost minimisation”) AND (analys* OR model*)
xi. “resource use” OR “resource utilization" OR “resource utilisation”
xii. (“treatment costs” OR “costs of treatment” OR “cost of treatment” OR “costs of therapy” OR “cost of therapy” OR “cost of treating”)
xiii. economic AND (evaluation* OR model)

Limits

- Publication period: 2000-2018
- Language: Dutch, French and German
- No animal studies:
  #4. Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh])
- No case reports and non-pertinent publication types:
  #5. case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt]

Number of hits PubMed (MEDLINE) ((#1 AND #2 AND #3) NOT (#4 OR #5)):

- 12 hits (02-10-2018)

Embase.com

#1 P: NERD/GERD

'non erosive reflux disease':ab,ti OR 'nonerosive reflux disease':ab,ti OR nerd:ab,ti OR 'gastroesophageal reflux disease':ab,ti OR 'gastrooesophageal reflux disease':ab,ti OR 'gastro-esophageal reflux disease':ab,ti OR 'gastro-oesophageal reflux disease':ab,ti OR gerd:ab,ti

#2 I: PPI therapy

'proton pump inhibitor'/exp OR 'proton pump inhibitor*':ab,ti OR ppi*:ab,ti OR omeprazole:ab,ti OR lansoprazole:ab,ti OR esomeprazole:ab,ti OR pantoprazole:ab,ti OR rabeprazole:ab,ti OR dexlansoprazole:ab,ti OR ilaprazole:ab,ti

#3 Ec: Economic evaluation

'economics'/de OR 'economic aspect'/de OR 'cost'/de OR 'health care cost'/de OR 'drug cost'/de OR 'hospital cost'/de OR 'socioeconomics'/de OR 'health economics'/de OR 'pharmacoeconomics'/de OR 'fee'/exp OR 'budget'/exp OR 'economic evaluation'/exp OR 'hospital finance'/de OR 'financial management'/de OR 'health care financing'/de OR 'low cost' OR 'high cost' OR health*care NEXT/1 cost* OR 'health care' NEXT/1 cost* OR fiscal OR funding OR financial OR finance OR cost NEXT/1 estimate* OR 'cost variable' OR unit NEXT/1 cost* OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti OR (cost* NEAR/3 (treat* OR therap*)):ab,ti OR health*care NEXT/1 (utilisation OR utilization) OR 'health care' NEXT/1 (utilisation OR utilization) OR resource NEXT/1 (utilisation OR utilization OR use)

Limits

- Publication period: 2000-2018
- Language: Dutch, French and German
- No case reports and non-pertinent publication types:
  #4. [article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [erratum]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim

Number of hits Embase.com ((#1 AND #2 AND #3) NOT (#4)):

- 7 hits (02-10-2018)

University of York CRD databases (DARE, NHS/EED and HTA databases)

- Language selection at CRD databased was not possible

9.2.5 Search filter for ethical issues

PubMed (MEDLINE)

#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18

#1 "Ethics"[Mesh]

#2 "Freedom"[Mesh]

#3 "Healthcare Disparities"[Mesh]

#4 health-care-delivery[majr] OR health-care-access[majr]

#5 "Informed Consent"[Mesh]

#6 "Morals"[Mesh]

#7 "Altruism"[Mesh]

#8 "Beneficence"[Mesh]

#9 "Ethicists"[Mesh]

#10 "Human Rights"[Mesh]

#11 "Ethics, Medical"[Mesh]

#12 quality of life[majr]

#13 (ethic*[tiab] OR moral*[tiab] OR bioethic*[tiab] OR complicit*[tiab] OR humanism[tiab] OR dignity[tiab] OR integrity[tiab] OR human-right*[tiab] OR principlism[tiab] OR normativ*[tiab] OR principle-base*[tiab] OR beneficence[tiab] OR autonomy[tiab])

#14 (non-maleficence[tiab] OR nonmaleficence[tiab] OR philosoph*[tiab] OR aristoteles[tiab] OR socrates[tiab] OR justice[tiab] OR fairness[tiab] OR hope[tiab] OR accessible[tiab] OR accessibility[tiab] OR Beauchamp[tiab] OR childress[tiab] OR equilibrium*[tiab] OR wide-reflective*[tiab] OR socratic[tiab])

#15 (social-shaping[tiab] OR casuistry[tiab] OR coherence-analy*[tiab] OR eclectic*[tiab] OR right-to-die[tiab] OR right-to-life[tiab] OR social-value*[tiab] OR ethnic-value*[tiab] OR personal-value*[tiab])

#16 (elsi[tiab] OR conviction*[tiab] OR harm[tiab] OR benefit-harm[tiab] OR harm-benefit[tiab] OR choice-of-end-point*[tiab])

#17 (rawls[tiab] OR rawlsian[tiab] OR utilitarian*[tiab] OR patient-choice[tiab] OR patient-decision-making[tiab] OR justify*[tiab] OR promise[tiab] OR imperative[tiab] OR normative[tiab] OR peril[tiab]OR conflicting-interests[tiab] OR equity[tiab] OR imperative[tiab] OR peril[tiab] OR promise[tiab] OR stigma[tiab] OR stigmatiz*[tiab] OR stigmatis*[tiab)

#18 (societal-value*[tiab] OR value*-of-society[tiab] OR fraud[tiab] OR falsified[tiab)

Embase.com

#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21

#1 ethics/exp

#2 freedom/exp

#3 health-care-disparity/exp

#4 health-care-delivery/mj or health-care-access/mj

#5 informed-consent/exp

#6 morality/exp

#7 altruism/exp

#8 beneficence/exp

#9 ethicist/exp

#10 human-dignity/exp

#11 human-rights/exp

#12 medical-ethics/exp

#13 personal-value/exp

#14 social-attitude/exp

#15 'quality of life'/mj

#16 (ethic* OR moral* OR bioethic* OR complicit* OR humanism OR dignity OR integrity OR human-right* OR principlism OR normativ* OR principle-base* OR beneficence OR autonomy):ti,ab,kw

#17 (non-maleficence OR philosoph* OR aristoteles OR socrates OR justice OR fairness OR hope OR accessible OR accessibility OR Beauchamp OR childress OR equilibrium* OR wide-reflective* OR so-cratic):ti,ab,kw

#18 (social-shaping OR casuistry OR coherence-analy* OR eclectic* OR right-to-die OR right-to-life OR social-value* OR ethnic-value* OR personal-value*):ti,ab,kw

#19 (elsi OR conviction* OR harm OR benefit-harm OR harm-benefit OR choice-of-end-point*):ti,ab,kw

#20 (rawls OR rawlsian OR utilitarian* OR patient-choice OR patient-decision-making OR justify* OR promise OR imperative OR normative OR peril OR conflicting-interests OR equity OR imperative OR peril OR promise OR stigma OR stigmatiz* OR stigmatis*):ti,ab,kw

#21 (societal-value* OR value*-of-society OR fraud OR falsified):ti,ab,kw

9.3 Study characteristics of two studies excluded from the efficacy, effectiveness and safety systematic review for the reason indirect comparisons

Reference	Country	Study design, study period	Study population	Intervention	Comparator	Sample size	Age (mean±SD in years)	Preliminary risk of bias
Tsai, 2004[16]	UK	Single-blind RCT NR (analysis in June 2002)	NERD	Continuous lansoprazole 15 mg (6 months)	On-demand esomeprazole 20 mg (6 months)	- Total: 622 - Intervention: 311 - Comparator: 311	- Intervention: 51 ± 13.8 - Comparator: 51 ± 13.8	Low risk of bias
Cibor, 2006[29]	Poland	Open-label RCT NR	NERD	Group 1: Continuous lansoprazole 15 mg (11 months)	Group 2: On-demand lanso-prazole 30 mg (11 months) Group 3: Inter-mittent therapy of 4-week course of lan-soprazole 30 mg, in case of recurrent symptoms (11 months)	- Total: 60 - Intervention: 20 - Comparator, group 2: 20 - Comparator, group 3: 20	- Intervention: 48 ± 11 - Comparator, group 2: 49 ± 12 - Comparator, group 3: 48 ± 13	High risk of bias

NR: not reported; SD: standard deviation

9.4 Overall Steps in the Full HTA

9.4.1 Efficacy, effectiveness and safety review

The systematic efficacy, effectiveness and safety review included in this scoping report will form the start of a full GRADE review (ref: GRADE Handbook and GRADEpro Guideline Development Tool [Software]).[22 23]

9.4.2 Cost effectiveness review

The development of a conceptual health economic model is essential as it identifies the information needs of the model and hence structures further research and data collection efforts.

The conceptual model needs to address those key parameters that drive both costs and health effects as well as their relation. The type of model will be chosen according to the clinical plausibility, key parameters identified as well as the data availability. We will follow the ISPOR modelling task force recommendations while conceptualising and populating the model.[44] Some additional complementary searches might be conducted in the full HTA phase and clinical expert input will be sought, if necessary both in the model population as well as the model validation steps.

Parametric uncertainty will be explored through probabilistic and one-way sensitivity analyses and structural/methodological uncertainty will be explored in several scenario analyses. Several subgroup (e.g. non-erosive, erosive reflux) analyses will be performed to see the health and cost impact of adoption of on-demand maintenance therapy with PPIs in relevant disease categories.

In addition to the health-economic model, a budget-impact model will be developed. The model will be checked by an independent modeller from iMTA, using the standard iMTA Quality Assurance (QA) protocol for models.

9.4.3 Ethical, legal, social and organisational domains review

Full-texts from the literature search will be screened together with clinical guidelines and narrative review studies that were identified in the clinical literature search.