The RELIEF-trial for patients with upper abdominal pain: study protocol for a randomized controlled trial to investigate the effectiveness of a web-based self-management tool compared with usual care for reduction of healthcare utilization and improvement of patient-reported outcomes

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Abstract

Background

Dutch healthcare faces increasing demand with constrained resources. Upper abdominal pain (UAP) is a highly prevalent symptom leading to substantial healthcare utilization and costs, with over 100,000 related hospital diagnoses annually in the Netherlands. In most cases, UAP is attributable to functional dyspepsia, irritable bowel syndrome, or symptomatic gallstone disease The overlapping symptom patterns of these diseases, which generally affect similar populations, leads to difficulties in diagnosing and an increased risk of exposing patients to unnecessary interventions and increase in healthcare costs.

Web-based education and lifestyle interventions are used in several high-prevalence disorders, but evidence supporting it is effectiveness for managing patients with UAP is lacking due to its heterogeneous diagnostic nature. This trial evaluates whether a web-based self-management tool can reduce healthcare utilization by improving patient education and diagnostic selection in UAP.

Methods

The RELIEF-trial is a multicenter, randomized, open-label superiority trial. Adult patients referred to hospital with UAP are eligible, except those with alarm symptoms. Participants are randomized to either usual care or the RELIEF intervention. Usual care is provided at the treating physician's discretion. The intervention group receives access to a web-based self-management tool prior to the first outpatient visit, providing structured information on UAP, treatment options, and lifestyle advice.

The primary outcome is the proportion of patients who will undergo diagnostic or treatment intervention within 12 months. Secondary outcomes include time to diagnosis, outpatient clinic- or emergency room visits, pain severity, imaging use (Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), morbidity and complications, and patient-reported outcomes.

Discussion

The RELIEF trial is the first randomized controlled trial comparing usual care with a web-based self-management tool in patients with UAP. It will assess whether web-based education improves self-management and safely reduces diagnostic and therapeutic interventions in patients without alarm symptoms.

Trial registration

Registry: ClinicalTrials.gov

Trial registration number: NCT06002516 (ClinicalTrials.gov),

Date of registration: 2023-08-21

Key words: upper abdominal pain, self-management, patient-reported outcomes, irritable bowel syndrome, functional dyspepsia

Background

Healthcare faces a major challenge due to increasing demand and limited staff and resources. Decision aids can help manage prevalent benign conditions with a mild course, such as upper abdominal pain (UAP), while reducing healthcare costs and utilization.

UAP is a common symptom that leads to significant burden with significant healthcare consumption and increase in costs. Dutch hospitals yearly diagnose over 100.00 patients cases of UAP.(1)

In most cases, UAP without alarm symptoms can be classified into functional dyspepsia (FD), irritable bowel syndrome (IBS) or symptomatic gallstone disease. Prevalence in the general population is 20%, 20-30% and 6-9%, respectively.(2-4) Alarm symptoms, including unexplained weight loss, persistent vomiting, lab abnormalities such as anemia of abnormal liver tests, or gastrointestinal bleeding, help differentiate between benign and malignant diseases, prompting more urgent investigation when present. With an incidence of 0,9%, malignancy is rarely uncovered in patients presenting with UAP.(5) (6) Symptomatic gallstone disease, FD, and IBS share overlapping symptom patterns and affect similar populations.(7) This overlap in symptoms between diseases can lead to ineffective diagnostic and therapeutic interventions.(8, 9)

A third of all upper gastrointestinal endoscopies are performed for dyspeptic symptoms. At the same time, the yield of endoscopy for this indication is low, and the procedure is unlikely to alter the clinical management of patients with dyspepsia.(10) Initiatives to reduce the use of upper gastrointestinal (GI) endoscopy for dyspepsia through guideline recommendations have led to better patient selection.(6, 11) Educational initiatives have been shown to positively influence patients' self-management and health-related decision-making.(6) Another example of a potentially ineffective intervention is a laparoscopic cholecystectomy (LC) in patients with abdominal pain and cholecystolithiasis, which fails to achieve anticipated pain resolution in only 20-30% of patients one year after surgery. Even after five year follow-up, only 60-80% of patients are pain-free.(12)

Traditional web-based education tools focus on a single disease. A more effective strategy would be a symptom-oriented approach, featuring a symptom assessment tool to differentiate between different UAP diagnoses and a decision aid for multiple treatment options.

This trial investigates if web-based education influences treatment choices in patients presenting with UAP by provision of a web-based self-management tool, the RELIEF pathway.
We hypothesize that the RELIEF pathway, safely accelerates the diagnostic pathway, promotes self-management and attributes to a more rapid reduction of symptoms, a more appropriate health care consumption and provides a basis for a lower number of ineffective diagnostic and therapeutic interventions.
Here we describe the development of a symptom-oriented education tool and the research protocol of the RELIEF-trial.

Methods

Study design and participants

The RELIEF-trial is designed as a randomized, multicenter, open-label, parallel-arm, superiority trial in seven Dutch hospitals.

Patients meeting the inclusion criteria are adults aged 18–70 years who are referred by their general practitioner for the diagnosis and/or treatment of upper abdominal pain. Exclusion criteria consist of alarm symptoms such as unexplained weight loss (>5 kg), persistent vomiting (>2x/day), gastrointestinal bleeding, or any other direct or indirect signs of cancer or upper GI tract bleeding (such as iron deficiency anemia) (table 1). Patients are contacted by the research physician to discuss participation, check eligibility and gain informed consent. Eligibility criteria are presented in Table 1. Data will be collected by the research physician in the participating hospitals.

This study protocol was developed and reported in accordance with the SPIRIT-guidelines.

Table 1 Eligibility criteria

Inclusion criteria	Age 18-70 years Referral with UAP to outpatient clinic of surgery or gastroenterology Sufficient command of the Dutch language to complete decision aids and fill out questionnaires Signed informed consent
Exclusion criteria	Alarm symptoms: Unexplained weight loss Persistent vomiting Gastrointestinal bleeding Any other direct or indirect signs of cancer or upper GI tract bleeding
	Other:

	Anemia Jaundice Pregnancy An expected life span of less than 12 months Known liver diseases A history of complicated cholecystolithiasis A history of inflammatory bowel disease A history of malignancy, except squamous cell carcinoma (SCC)/basal cell carcinoma (BCC) First or second degree relative with history of upper GI malignancy

Outcomes

The primary endpoint is defined as the proportion of patients who will undergo an invasive diagnostic or treatment intervention for UAP within 12 months follow-up. Interventions are defined as upper and lower gastrointestinal (GI) endoscopies and cholecystectomies.

Secondary endpoints include count-based healthcare utilization measures; the total number of diagnostic and therapeutic interventions, outpatient clinic visits, emergency room visits, and hospital admissions for UAP within 12 months, as well as the time until diagnosis, diagnostic imaging (abdominal ultrasound, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)), and condition- and intervention-related morbidity and complications. Patient reported outcomes and treatment satisfaction will be assessed at baseline and during follow-up.

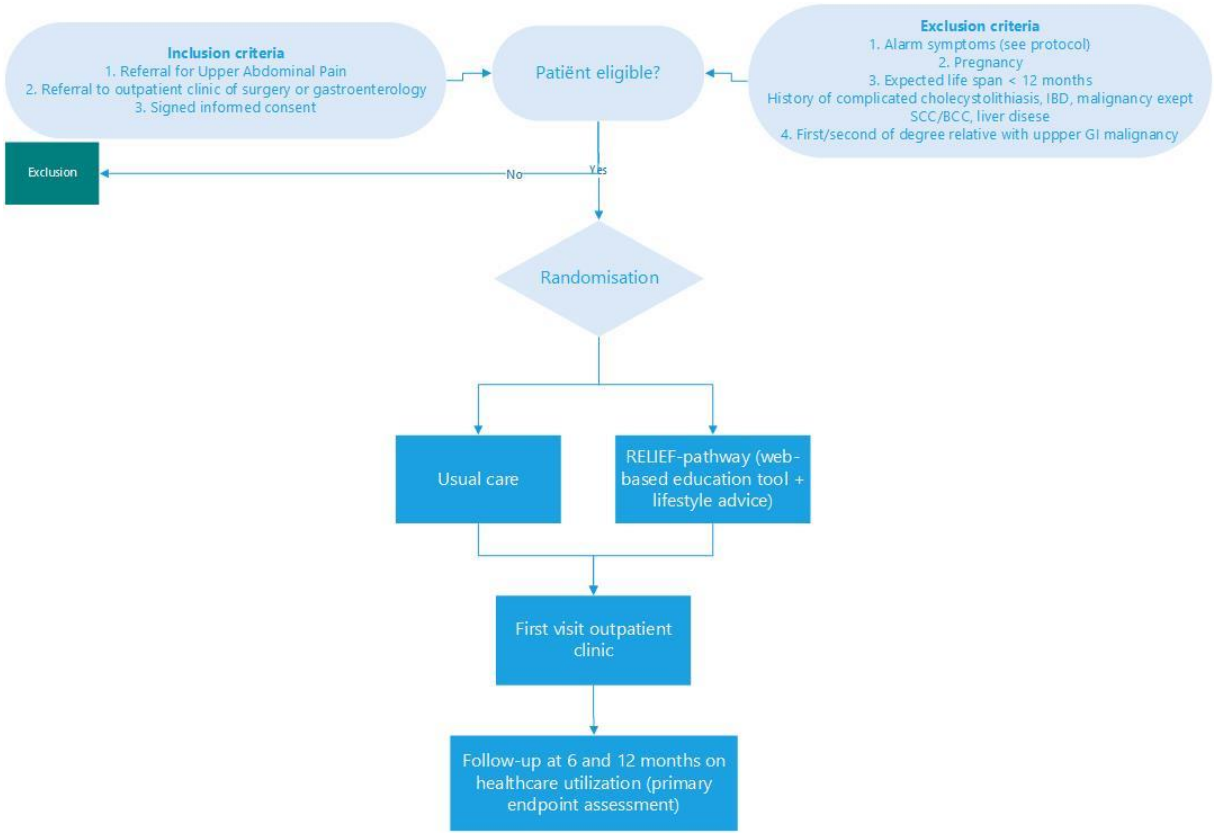
Table 2 overview of reported morbidity and complications

Gallstone-related complications	**Missed or delayed diagnoses**
Cholecystitis	Malignant gastrointestinal neoplasm
Choledocholithiasis	Gastrointestinal hemorrhage
Cholangitis	Inflammatory Bowel Disease
Biliary pancreatitis	

Randomization

Stratified cluster randomization will be done by computer- and web-based (Castor EDC) to ensure an even distribution in the two arms of the study (usual care versus web-based educational tool). Stratification will be done by participating center and medical specialism; surgery or gastroenterology. Inclusion, randomization and management are illustrated in fig. 1. Tere will be no blinding involved.

Figure 1: Inclusion and exclusion flowchart



Usual care

Patients assigned to the usual-care group will receive usual care and will be treated according to the physician's knowledge and preferences at participating centers.

Intervention (the RELIEF-pathway)

In the intervention arm, patients will be informed about the use of the self-management tool. Patients receive access to the tool prior to their visit to the outpatient clinic. Completion of the intervention will be monitored using automatically recorded usage data from the web-based tool, including login moment and progression through the individual modules. Usage data will be extracted directly from the platform's backend logging system. Adherence will be defined as completion of all core components of the intervention (steps 1–5 of the self-management tool). Outcomes will include the proportion of participants initiating the tool and the proportion achieving full completion. Intervention adherence will be included in secondary analyses. Additionally, an optional lifestyle consultation at a specialized outpatient clinic is offered and patients are provided with comprehensive guidance to initiate and engage lifestyle changes and adopt a healthier lifestyle.

The RELIEF self-management tool

The RELIEF self-management tool was designed and developed in collaboration with PatientPlus, physicians, patients, and the Dutch Digestive Foundation (MDL Fonds), a patient representative organization supporting individuals affected by gastrointestinal diseases. PatientPlus served as a non-commercial infrastructure partner and was responsible for the technical development, hosting, deployment, and user interface design of the patient-facing web-based tool. The clinical content was developed by the study investigators in collaboration with domain experts in the three main causes of upper abdominal pain addressed in the RELIEF pathway. Patients and the MDL Fonds provided input to support patient relevance and usability. The information was independently reviewed by Stichting Makkelijk Lezen to improve readability and accessibility for Dutch patients. PatientPlus had

no role in data analysis, interpretation, or study outcomes, and no commercial interests influenced the design, content, or evaluation of the intervention. The self-management tool is in Dutch and available via Informatie - Keuzehulp.

The tool comprises a self-management guide containing information on the potential diagnosis FD, IBS and uncomplicated cholecystolithiasis. The tool contains a survey about symptoms to differentiate between UAP diagnosis, a symptom assessment tool. Secondly, information on upper GI tract endoscopy, colonoscopy, and laparoscopic cholecystectomy is provided.
Finally, the tool offers guidance on lifestyle modifications to reduce UAP. This information is based on clinical guidelines and expertise of the lifestyle coaches. (13-15)

The tool consists of five steps:

1. Information about UAP and a symptom assessment tool.
2. Lifestyle education
3. A decision guide
4. A section with disease-specific information
5. A personalized conclusion and treatment advise

The layout of the tool is displayed in Fig. 2 (insert figure here)

The lifestyle assessment is provided by trained lifestyle coaches from the Department of Prevention and Lifestyle at Radboudumc Nijmegen and, where available, by designated lifestyle coaches at participating centers. To ensure standardization, all coaches follow a shared protocol based on national lifestyle counselling guidelines, including a structured two-visit assessment format followed by tailored lifestyle advice for implementation in the patient's home environment.
Referral to lifestyle coaching is optional and part of regular care. Participation, attendance, and completion of lifestyle coaching sessions are prospectively recorded in the study database to allow

assessment of intervention exposure and adherence. Lifestyle coaching will be reported descriptively and, if numbers allow, used in sensitivity analyses comparing outcomes according to coaching participation and completion status.

Follow-up and assessment timing

The total duration of follow-up per patient will be 12 months, after which data collection will take place. Data collection per patient will start 12 months after inclusion. Besides regular questionnaires (table 3), no follow-up assessments will be performed by the investigators.

Questionnaires

Patient-reported outcomes will be assessed at four time points via a web-based application; at baseline, the day of visit of the outpatient clinic and at 6- and 12-months after randomization. Patients will receive a reminder and a telephone call to promote participant retention if there is no response. The surveyed questionnaires are summarized in Table 3.

Table 3 Overview of questionnaire

Questionnaire	Outcome measure	Details	Baseline	1 month	6 months	12 months
The Patient Assessment of Gastrointestinal Disorders Symptoms Severity Index (PAGI-SYM) **(16)**	Disease related complaints	20-item symptom severity measure on common GI symptoms in patients with gastroesophageal reflux disease (GERD), dyspepsia and gastroparesis.	x	x	x	x

Izbicki pain score **(17)**	Evaluation of pain	4-item questionnaire measuring pain.	x	x	x	x
Short Health Anxiety Index measures health-related anxiety (SHAI) **(18)**	Evaluation of health related anxiety	18-item questionnaire assessing health anxiety independent of physical health status.	x	x	x	x
Shared-decision making (SDM-Q-9) **(19)**	Shared decision making	9-item questionnaire developed to measure the extent to which patients are involved in process of decision-making	x	x	x	x
Medical Consumption Questionnaire (iMCQ) **(20)**	Medical consumption	17-item questionnaire related to contacts with health care providers.	x		x	x

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233 **Sample size**

234 Based on current Dutch clinical practice, it is estimated that 80% of referred patients with UAP
235 undergo an intervention, such as an endoscopy or laparoscopic cholecystectomy or an additional
236 hospital visit, within a 12-month follow-up period. (6) The RELIEF pathway is hypothesized to reduce
237 the intervention rate by 30%, based on the results of the C-GALL-trial and the TRIODE-trial. (6, 21)
238 Separate sample size calculations were performed for the three distinct diagnoses, targeting a 30%

reduction in colonoscopies for IBS, gastroscopies in dyspepsia, and laparoscopic cholecystectomies in uncomplicated gallstone disease. (22, 23) To detect this effect with 90% power at a two-sided alpha level of 1.7% (Bonferroni correction because of 3 diagnostic groups), a Chi-Square test for two proportions, with 1:1 randomization stratified by center and department and using permuted blocks, a sample size of 2 × 71 patients per group is required (calculated using G*Power, version 3.1.7, June 2023). Accounting for a potential 10% loss to follow-up, a total of 157 patients per diagnostic group will be enrolled, resulting in an overall trial sample size of 471 patients.

Safety monitoring

Trial participants in the control arm receive usual care, and those in the intervention arm are provided with access to the education tool, but they also visit the outpatient department. The diagnostic interventions and eligible treatment pathways are based on current guidelines and do not alter the standard of care. In the tool, patients are advised to consult the outpatient lifestyle clinic, but the consultation is voluntary and not required within the intervention arm. Therefore, the risk of participating in the intervention-arm of this trial is negligible, and the use of a Data Safety Monitoring Board (DSMB) was not deemed necessary by the medical ethics committee.

Data confidentiality and participant privacy protection

Personal information will be collected by trained research staff and stored in a secure, password-protected electronic database (Castor EDC) using unique study IDs. Identifiable data are stored separately and only accessible to authorized personnel. All data are handled in accordance with GDPR and Dutch privacy regulations and are stored in pseudonymized form on secure institutional servers before, during, and after the trial.

Statistical analysis

Data will be analyzed according to the intention-to-treat principle. In all analyses, statistical uncertainties are expressed in 95% two-sided confidence intervals. A two-tailed p-value <0.05 will be considered statistically significant.

Demographic and baseline characteristics

For intervention and control group, data on demographic and baseline characteristics will be summarized for continuous variables, in case of normal distribution by means and standard deviations, and in case of non-normal distribution by medians and interquartile ranges. For discrete variables data (eg. sex, socio-economic status) will be summarized by frequencies and proportions. Correlations will be calculated using Pearson's r in case of normally distributed data and Spearman's rank test for non-normally distributed data.

Because of randomization, balanced groups are expected. For those control variables that are not balanced we will include them in the multivariate analyses determine their effect on the treatment effect on primary and secondary outcomes.

Primary and secondary outcomes

To assess the treatment effect on our primary outcomes, logistic regression analyses (intervention performed yes/no) will be performed. For the primary outcome a logistic regression analysis will be performed. In addition, the primary outcome will be analysed separately within each of the three diagnostic groups (functional dyspepsia, irritable bowel syndrome, and uncomplicated symptomatic gallstone disease), using the same logistic regression approach; the trial was individually powered for each diagnostic group (see Sample size). Count-based secondary healthcare utilization outcomes will be analysed using appropriate regression models for count data.

To analyze the treatment effect on the secondary outcomes, appropriate regression analyses will be performed, based on the underlying distribution of that secondary outcome.

To compare change over time of questionnaire data between intervention and control, we will use mixed model analyses with baseline and follow-up data as outcome and assessed time by randomization group interaction.

Ethical consideration and informed consent

This study will be conducted according to the principles of the Declaration of Helsinki (60th version, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other applicable guidelines, regulations, and Acts. Ethical approval was obtained from the Medical Research Ethics Committee (MEC) of the Radboud University Medical Center Nijmegen (Approval no. 2023-16667, Date: 15-08-2023). As this study concerns non-WMO research, the scientific offices of the participating centers did not perform separate ethical reviews, but formally aligned with the approval issued by the MEC Nijmegen. No separate approval numbers were issued by local committees, as this requirement was waived where applicable. No additional documentation exists. Informed consent will be obtained from each participating patient in both oral and written or digital form prior to randomization, at the moment of referral to the hospital. Both corresponding authors will have access to the final trial dataset.

Discussion

Rationale of this study

The RELIEF trial is the first randomized controlled trial to investigate the effectiveness of a web-based self-management tool in patients with UAP, compared to standard-care in order to safely reduce healthcare consumption. This trial aims to address the gap in current healthcare approaches for UAP, where overlapping symptom patterns from FD, IBS, and gallstone disease often lead to ineffective diagnostic and therapeutic interventions. By providing patients with a comprehensive, symptom-oriented tool that combines education on UAP, lifestyle modification, and treatment options, we hypothesize that the RELIEF pathway will improve patient self-management, reduces unnecessary

healthcare utilization and is safe to apply. The results of this trial could potentially redefine the management of UAP, more efficient approach to treatment and care, while ensuring patient safety, regarding complications and morbidity.

The inefficiency of interventions in a significant number of patients with UAP, together with the lack of evidence regarding the optimal treatment, underscores the need for a more evidence-based approach to manage the high volume of care requests. FD and IBS frequently co-occur in patients with uncomplicated gallstone disease, complicating pain relief efforts. Additionally, one-third of patients eligible for cholecystectomy also meet the criteria for FD or IBS, and more than 20-30% continue to experience pain after cholecystectomy. (22) Improved patient selection, particularly through a validated prediction model for patients with gallstones and upper abdominal pain, has been shown to lead to better outcomes. Previous studies illustrate that dyspepsia is one of the most common incorrect indications for gastroscopy. (11, 24) In the TRIODE-trial, introduction of a decision aid and self-education tool for patients with dyspepsia was shown to effectively reduce the number of unnecessary gastroscopies by 43%. (6)

These findings highlight the importance of incorporating symptom-dependent outcomes into shared decision-making.

Rationale of this design

In this study, a pragmatic approach was chosen to investigate a self-management tool in patients with UAP. The randomized controlled open-label superiority design emphasizes patient empowerment by providing information on potential self-help strategies and the impact of invasive diagnostics and treatments, rather than focusing solely on treatment effectiveness.

Different alternative designs were considered, but were deemed unsuitable for several reasons. A design which randomized patients to undergo or not undergo a diagnostic or treatment procedure, overlooked the core issue of this proposal. The focus here is on a novel design that integrates a

decision aid with a symptom assessment tool, emphasizing self-help, disease insight, and lifestyle improvements as an important first treatment option.

A stepped-wedge design would focus on the population and center-specific procedures, and not on the individual level of the patient. Research goals would then be process evaluation, implementation and inter-hospital effects. This design would not fit the goal to reduce individual healthcare utilization, while maintaining patient reported outcomes.

A potential pitfall of the present design is the voluntary consultation of the lifestyle coach. This could lead to selection bias, as only patients who are more motivated or have a greater interest in lifestyle changes may choose to consult the coach and achieve other outcomes. Additionally, approaching patients at the time of referral from the general practitioner and prior to the first outpatient visit introduces a selection, with a risk of bias and dropout.

Impact of the RELIEF-trial

The combined knowledge outlined in the rationale of this study has been integrated into a decision aid for patients with UAP, merging medical expertise with lifestyle advice and education. This holistic approach focuses on self-management to reduce unnecessary and ineffective healthcare utilization while enhancing patient empowerment. Additionally, with the potential future implementation of the tool in primary care, unnecessary referrals could be reduced, contributing to more efficient healthcare delivery.

The RELIEF trial is a multicenter, prospective study designed to evaluate the impact of a web-based symptom checker with a self-management tool and lifestyle advice, in patients with UAP. This trial aims to reduce healthcare utilization through optimizing self-management and improve patient-reported outcomes. As such, the RELIEF trial has the potential to influence daily clinical practice and provide valuable insights for (inter)national guidelines on the optimal management of UAP.

List of abbreviations:

CT Computed tomography

FD Functional dyspepsia

GI Gastrointestinal

IBS Irritable bowel syndrome

ICMJE International Committee of Medical Journal Editors

IQR Interquartile range

MEC Medical Research Ethics Committee

MRI Magnetic resonance imaging

RCT Randomized controlled trial

SD Standard deviation

SPIRIT Standard Protocol Items: Recommendations for Interventional Trials

UAP Upper abdominal pain

WMO Medical Research Involving Human Subjects Act (Netherlands)

Declarations

Ethics approval and consent to participate

Ethical approval for this study was obtained from the Medical Research Ethics Committee (MEC) of the Radboud University Medical Center Nijmegen (2023-16667 Date: 15-08-2023). Informed consent was obtained from all participants prior to inclusion.

Consent for publication

Not applicable. This manuscript contains no identifiable individual participant data.

Availability of data and materials

The datasets generated and/or analyzed during the current study will be available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no financial or non-financial relationships or activities that could be perceived as a potential conflict of interest in relation to this work. PatientPlus provided non-commercial technical infrastructure support for the RELIEF self-management tool but had no role in the study design, clinical content, data analysis, interpretation, or reporting. The authors declare no competing interests.

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Authors' contributions

A.J. and P.R.d.R. conceived the study. A.J., D.J.C., and P.R.d.R. designed the methodology. A.J. drafted the manuscript. All authors contributed to data collection, critically revised the manuscript, and approved the final version.

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AI statement

No artificial intelligence tools were used in the preparation of this manuscript.

Trial status statement

Recruitment started on 1-11-2024 and is currently ongoing. At the time of submission, 58 of a planned total of 471 participants have been enrolled. Recruitment is not yet complete. Participants are currently in active follow-up.

Related publications

We confirm that no related articles based on this protocol have been published or are currently under consideration elsewhere.

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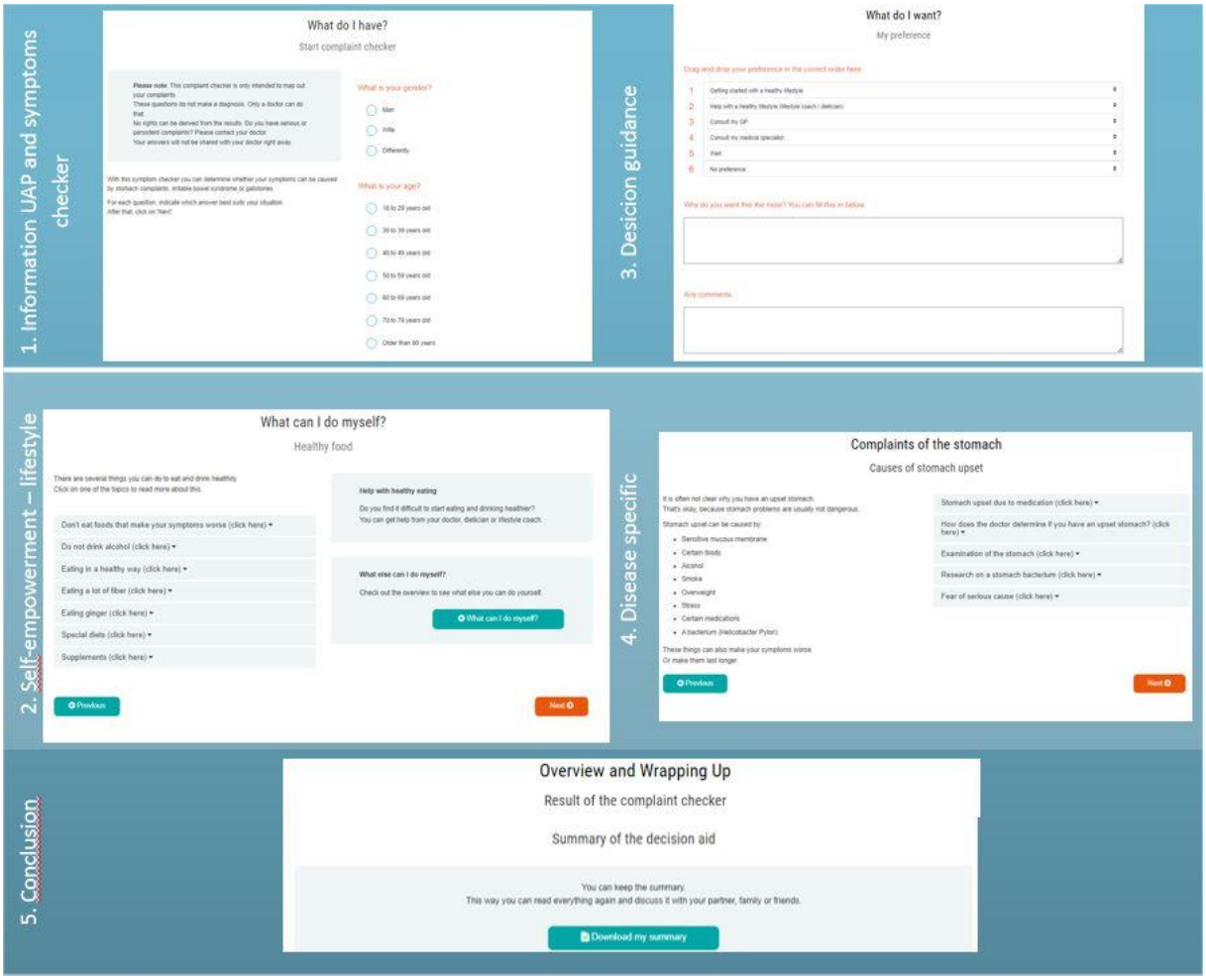


Figure 2: overview of web-based education tool