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Longitudinal outcome monitoring in patients with chronic gastroduodenal symptoms investigated using the Gastric Alimetry™ system

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PROTOCOL

Longitudinal outcome monitoring in patients with chronic gastroduodenal symptoms investigated using the Gastric Alimetry™ system

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Authors' contributions: CV, ND, AG, GOG drafted the manuscript. GS, KM, SC, AG, GOG supervised the protocol design and final manuscript. All authors contributed to the final drafting and review of the manuscript.

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Abstract

Introduction

The Gastric Alimetry™ platform offers a multimodal assessment of gastric function through body surface gastric mapping (BSGM) and concurrent symptom-tracking via a validated App. We aim to perform a longitudinal cohort study to examine the impact of Gastric Alimetry, and changes in clinical management on patient symptoms, quality of life, and psychological health.

Methods

This is a prospective multicentre longitudinal observational cohort study of participants with chronic gastroduodenal symptoms. Consecutive participants undergoing Gastric Alimetry™ will be invited to participate. Quality of life will be assessed via EuroQol-5D and the Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL) score. Gastrointestinal symptoms will be assessed via the Patient Assessment of Upper Gastrointestinal Symptom Severity (PAGI-SYM) index, and the Gastroparesis Cardinal Symptom Index (GCSI). Psychometrics will be assessed, including anxiety via the General Anxiety Disorder-7 (GAD-7), perceived stress using the Perceived Stress Scale 4 (PSS-4), and depression via the Patient Health Questionnaire 9 (PHQ-9). Clinical parameters including diagnoses, investigations, and treatments (medication and procedures) will also be captured. Assessments will be made the week after the BSGM test, at 30-days, 90-days, 180-days, and 360-days thereafter.

Analysis

The primary outcome is feasibility of longitudinal follow-up of a cohort that have undergone Gastric Alimetry™ testing; from which patients' continuum of care can be characterised. Secondary outcomes include changes in patient-reported symptoms, quality of life, and psychometrics (anxiety, stress, and depression). Inferential causal analyses will be performed at the within patient-level to explore causal associations between treatment changes and clinical outcomes. The impact of Gastric Alimetry on clinical management will also be captured.

Ethics and dissemination

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The protocol has been approved in Aotearoa New Zealand by the Auckland Health Research Ethics Committee (AHREC). Results will be submitted for conference presentation and peer-reviewed publication.

Registration

Submitted to the Australian New Zealand Clinical Trials Registry (ANZCTR) at the time of submission.

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Introduction

Body surface gastric mapping (BSGM) using the Gastric Alimetry™ System is a breakthrough diagnostic modality for the assessment of gastric function.(1–6) BSGM has found utility in defining underlying aetiologies within a diverse array of cohorts including patients with chronic gastroduodenal symptoms, type 1 diabetes, delayed gastric emptying, and post-gastric surgery.(2,3,7,8) Validated metrics of gastric function and simultaneous symptom-capture is also emerging as a tool to enable clinicians to make decisions based on objective and actionable biomarkers,(9–11) rather than the trial-and-error therapies pervasive in these poorly understood gastroduodenal disorders. In a recent series of patients assumed to have intestinal failure secondary to gut dysmotility, BSGM informed care in 100% of patients, offered an updated diagnosis in 60% and facilitated a cost-saving wean from parenteral nutrition in two thirds of patients.(11)

Longitudinal data capture is required to assess the impact that Gastric Alimtery™ has on long-term care and clinical outcomes. A scalable data platform to rapidly accrue longitudinal data is required to track changes in symptoms, quality of life, and psychological outcomes over time. These data will form the basis of future assessments of treatment decisions at scale. Once such a data platform is established, over time a large repository of longitudinal data will be available to compare the impacts of investigations, medication changes, and procedural interventions on patient outcomes. Such causal inferences can lay the foundation for future randomised trials, with potential to open new avenues for data-driven research within care paradigms in gastroduodenal health.

This manuscript outlines a study protocol for the establishment of a longitudinal data capture system in this context, including a) data and outcomes being collected, time course of collection, and rationale; b) a detailed overview of data linkage strategies that enable multimodal and ongoing data capture; and c) data management and infrastructure to facilitate ongoing analytics.

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Methods

This protocol is described in accordance to the relevant items of the SPIRIT checklist (Standard Protocol items: Recommendations for Interventional Trials).(12)

Study objectives

At the time of the initial Gastric Alimetry™ test, comprehensive gastrointestinal disorder, quality of life, and psychometrics assessments will be completed. This study aims to follow up all consenting participants undergoing Gastric Alimetry™ testing over a period of one year to assess changes in self-reported symptoms, quality of life, anxiety, stress, and depression measures, and changes in clinical care (including investigations initiated after Gastric Alimetry™ testing, and treatments started or changed). We aim to generate a database of patients to assess within-subject changes with regards to relevant clinical management initiated on the basis of Gastric Alimetry™ in patients with chronic gastroduodenal symptoms.

Study design

This is a prospective, multicentre, longitudinal, observational cohort study that will occur via the BSGM Consortium (an international network of collaborators performing Gastric Alimetry™ tests). Auckland, New Zealand will be the lead site; other recruiting centres at this stage include Calgary, Canada; and Western Sydney, Australia. Further sites are eligible to enrol at any time.

Study setting

Any site performing Gastric Alimetry™ tests is eligible to participate. Each site uses a standardised Gastric Alimetry™ App through which patient-level expressions of interest will be obtained. Thereafter, interested participants will be registered onto the REDCap system, where informed digital consent for participation will be sought, after which standardised study questionnaires will be administered. Participants will receive surveys via MyCap, a participant-facing app linked with REDCap.

Sample size and power calculation

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The broader aim of this study is to develop a database of participants with chronic gastroduodenal symptoms that follow a range of real-world clinical management pathways. Formal evaluations of causal links between clinical diagnoses, investigations, and management to changes in patient-reported symptoms, quality of life, and psychometrics will ultimately require randomised controlled trials. However, data accrued from this longitudinal follow-up will inform power calculations for subsequent pre-specified research questions. In a cohort of symptomatic patients, a difference between means of 0.1 in the EQ-5D index corresponds to a sample size of 100 participants with an alpha of 0.05 and power of 0.8.(13) In the establishment phase we anticipate 100 participants to be recruited during March to December 2023, who will have completed the one year of follow-up by December 2024. Thereafter, further data collection is expected, with large-scale expansion to power further analytics.

Data collection and management

All data will be collected prospectively and stored online in an encrypted format through a secure Research Electronic Data Capture (REDCap) web server hosted by the University of Auckland.(14). Initial and all subsequent surveys will be administered using MyCap, a participant-facing mobile application integrated with REDCap.(15).

Eligibility criteria

All adults aged 18 years and above consenting to a Gastric Alimetry™ test are eligible for inclusion. Exclusion criteria include age <18 years, history of skin allergies or a history of extreme sensitivity to cosmetics or lotions, and vulnerable groups such as prisoners, individuals known to have cognitive impairment or institutionalised individuals. No exclusions will be made based on the clinical management of patients as, for each intervention, a series of 'exposed' and 'controlled' participants will be required to assess causal relationships. Healthy volunteers that consent can also be included to form a comparator arm for analyses.

Participant informed consent process

All individuals undergoing a Gastric Alimetry™ test will be invited to participate in the study via the Gastric Alimetry™ App. Those who express interest will be loaded onto the REDCap system and will receive a REDCap-initiated digital consent form. Those who provide informed consent via an e-

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signature will be loaded into MyCap, enrolled into the study, and issued a unique study identification number within REDCap that is linked to their MyCap and Gastric Alimetry™ records.

Outcomes

Quality of life will be assessed via EuroQol-5D (EQ-5D) and the Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL) score. Gastrointestinal symptoms will be assessed via the Patient Assessment of Upper Gastrointestinal Symptom Severity (PAGI-SYM) index, and the Gastroparesis Cardinal Symptom Index (GCSI). Anxiety will be assessed through the General Anxiety Disorder-7 (GAD-7),(16) perceived stress using the Perceived Stress Scale 4 (PSS-4),(17) and depression via the Patient Health Questionnaire 9 (PHQ-9).(16) Clinical parameters including, diagnoses (Gastric Alimetry™ phenotype, Rome-IV diagnosis),(18) investigations (gastric emptying, transit studies, manometry, endoscopy), and treatments (medications, and procedures), as well as changes in the above measures, and date of change will also be captured. A comprehensive overview of the data being collected at each time point is overviewed in **Figure 1**.

Gastrointestinal symptoms

At each of the post-test time points (index test, 30-days, 90-days, 180-days and 365-days), participants will be asked to complete a daily symptom diary for seven days. Each evening, they will rate the severity of seven gastrointestinal symptoms over the past 24 hours. Each symptom is rated using a 0–10 Likert scale, with anchors at 0 “none,” indicating no symptom experience, and 10 indicating the “most severe imaginable” extent of a symptom experience. The rating is determined by the worst symptom experience in the past 24 hours for each symptom. The symptoms are stomach burn, stomach pain, nausea, bloating, postprandial fullness, early satiation, belching, and number of vomiting events. An additional rating distress arising from excessive belching is included, using a 0-10 Likert scale, with anchors at 0 “none,” and 10 “worst imaginable bother.” **Figure 2** shows an example of the MyCap interface for symptom ratings.

This symptom questionnaire is adapted from the basis the Functional Dyspepsia Symptom Diary (FDSD) and follows the recommended 24-hour recall period to minimise recall bias and account for day-to-day variation.(19) The questionnaire follows similar principles to the The American

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Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index Daily Diary (ANMS GCSI-DD), which recommends using one-week blocks for baseline and follow-up symptom scoring and completion of the diary at the same time each evening, prior to bedtime, to capture the patient's experience after all of the day's meals.(20)

Psychometric and Quality of Life Questionnaires

During the index Gastric Alimetry™ test, participants will complete the EQ-5D and PAGI-QOL questionnaire, and at each follow-up time point, the EQ-5D will be completed. The EQ-5D, a questionnaire on health-related quality of life, was chosen for its wide acceptance, brevity, and advantages for cost-utility analyses.(21,22) To quantitatively assess self-reported anxiety, stress, and depression symptomatology, widely validated and accepted psychometric tools will be administered, including the GAD-7,(16) PSS-4,(17) and PHQ-9 respectively.(16) These will be administered once per time point, unlike the repeating symptom diaries.

Clinical management / interventions

The following investigations, clinical management decisions, and treatments will be captured to facilitate observational analyses of causal hypotheses.

- Investigations
    - Imaging: X-ray, ultrasound, computed tomography scans, magnetic resonance imaging, vascular imaging, BSGM, scintigraphy, antro-duodenal manometry
    - Specialised blood tests: coeliac serology, H pylori stool PCR, alpha-1-antitrypsin, ceruloplasmin, liver function tests, IgA, lactose tolerance test, thyroid function tests
    - Endoscopy: esophagogastroduodenoscopy +/- biopsy
- Referrals
    - Specialist or referral to another service (e.g., psychiatry, surgery, endocrinology etc.)
- Treatments
    - Non-pharmacological: lifestyle modifications (e.g., initiating an exercise program), change in diet, counselling (in-person, virtual, app-based), psychotherapy (e.g. cognitive behavioural therapy, acceptance commitment therapy, mindfulness, hypnosis, relaxation therapy; in-person, virtual, app-based)

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- Medications: neuromodulator, prokinetic, antiemetic, anxiolytic, PPI, H2-receptor antagonist, other
- Endoscopic procedures: gastric peroral endoscopic myotomy (G-POEM), pyloric botox
- Surgery: anti-reflux surgery, gastrointestinal resection, small intestinal diversion

Follow-up

Immediately following the Gastric Alimetry™ test, participants will complete a daily symptom diary each evening for seven-days. At 30-days post-test, participants will complete a combined psychometric and quality of life questionnaire, followed by seven days of daily symptom diaries. This combination of psychometrics, quality of life, and symptom questionnaires will repeat at 90 days, 180 days, and 360 days (**Figure 3**). The MyCap system will remain open for patients to enter changes in diagnosis or management in consultation with their clinical care team (including the research team at the discretion of the recruiting sites).

To encourage engagement, participants will be able to use their own mobile phones to access MyCap's patient-centred interface. To facilitate successful follow-up and data completeness participants will be sent scheduled text message or email reminders to complete questionnaires using Twilio, a third-party REDCap add-on. Twilio is a messaging platform that allows SMS messages to be programmatically scheduled and sent worldwide.(23) Questionnaire timing will be scheduled based on individual patient timelines, customised using the date of initial Gastric Alimetry™ test.

Statistical analysis

This protocol describes the development of a standardised and scalable data platform for tracking changes in symptoms, quality of life, and psychological outcomes over time. Exploratory and pilot analyses will be performed within acknowledged limitations of a non-randomised study design. Longitudinal assessments allow for the evaluation of the efficacy and utility of diagnostic assessments and treatments offered to patients. Monitoring within-subject changes has been shown to offer advantages in establishing causal relationships.(24) As data accrues over time, a large repository of longitudinal data will be available to compare the impacts of investigations, medication changes, and

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procedural interventions on patient-reported outcomes. Such causal inferences can lay the foundation for future randomised trials, informing power calculations, and identifying research priorities.

Preliminary analyses will include descriptive comparative statistics, such as univariate between-group comparisons and also before-after testing (using individuals as their own control), where pre- and post-intervention paired statistics will be employed. Normally distributed data will be reported as mean (SD), and non-normally distributed data as median (IQR). Statistical comparisons will be performed using independent samples t-tests, analysis of variance (ANOVA), paired-samples t tests, or repeated measures ANOVA for normally distributed variables; Mann-Whitney U, Kruskal-Wallis tests, Wilcoxon signed-rank test, or Friedman's test for non-normally distributed continuous or ordinal variables; and $\chi 2$ tests or McNemar's test for categorical variables. Regression models will be used as appropriate for relevant outcomes including multivariate linear regression with adjustment for relevant demographic confounders. If sample sizes allow, mixed effects hierarchical models will be employed to account for natural clustering structures e.g., at the centre-level. Model selection will be guided by parsimony, clinically plausible relationships between predictors and outcomes, and minimisation of the Akaike information criterion.(25) Missing data will be interrogated to assess if they are missing at random, and multiple imputation by chained equations or pairwise deletion will be employed as appropriate.

Study delivery and quality assurance

This longitudinal cohort study will be centrally managed by a steering group consisting of expert statisticians, data managers, and clinician scientists with oversight and guidance from key opinion leaders in the field of gastroenterology and gastrointestinal surgery. Regular data-auditing will be performed with communication between the steering group and individual sites. Training resources are available to ensure standardised use of the Gastric Alimetry™ system for all device users.(26)

Patient and public involvement

Several rounds of patient interviews were completed during the development stage of the Gastric Alimetry™ platform,(6,27) which informed the design and delivery of the app. Patient feedback will be actively sought at the time of each test and will contribute to ongoing development and data

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applications. Interviews with a range of patients, and gastric disorder patient advocacy group leaders have informed relevant study designs and key clinical questions; most relevant to this protocol being the impact on individual patient's continuum of care to reduce investigations, offer more actionable diagnoses, relationships to psychological health variables, and to direct more efficacious therapies.

Ethics and dissemination

Ethics approvals have been sought according to the requirements of each participating centre. At the lead site, the protocol has been approved in Aotearoa New Zealand by the Auckland Health Research Ethics Committee (AHREC; ref AH1130). Results will be submitted for conference presentations and peer-reviewed publication.

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Discussion

Gastric Alimetry™ is emerging as a significant new clinical test of gastric function combining gastric electrophysiology and concurrent symptom tracking.(1,6) This diagnostic tool offers a new paradigm for the investigation and management of patients with chronic gastroduodenal disorders,(2) but longitudinal data on outcomes is now required to define its impact on clinical workflows, diagnoses, and outcomes. Here we present a longitudinal cohort study protocol to assess the impact of Gastric Alimetry™ on patients' continuum of care; this will offer robust data for assessing relationships between clinical diagnoses, and management decisions on patients' symptoms, psychological symptomatology, and quality of life. These observational data will guide hypothesis testing, facilitating prioritisation and powering of future trials to advance the field.

This study also aims to generate evidence in support of putative mechanisms for poorly understood gastroduodenal symptoms in line with Tack et al's plausibility criteria for disease mechanisms in functional gastrointestinal disorders.(28) The longitudinal study design in particular is essential to generate evidence for the fifth putative criterion within this framework: 'Therapeutic response'/'Congruent natural history', which states that treatment aimed at correcting an underlying disorder improves symptoms, or, changes in symptom severity parallel changes in the severity of the disturbance.(28) This evaluations are also in-line with innovation frameworks which recommend large-scale longitudinal surveillance of outcomes when novel medical innovations such as the Gastric Alimetry™ system are employed in routine clinical use.(29,30)

We developed an integrated digital platform for robust data-linkage, accurate, and secure storage of longitudinal, repeated measures data. REDCap serves as the secure data storage infrastructure with the mobile MyCap app being the patient-facing platform for collecting patient-reported outcomes. Data completeness is encouraged through the use of Twilio, enabling automated, scheduled reminders. Scheduled tasks personalised to each individual patients' timelines facilitate scalability to a large volume of patients.(31) These data are then linked to gastric electrophysiological signal data after refined artefact rejection and algorithmic post-processing,(32) and the Gastric Alimetry™ App data which are stored on a HIPAA-compliant cloud platform.(33)

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Strengths and limitations

This study utilises validated, widely used instruments to measure self-reported gastrointestinal symptoms, quality of life, and psychological factors. Validated questionnaires were chosen for their external validity, brevity so as to be pragmatic with data collection, and reduced burden on patients. The use of self-administered questionnaires and diaries have also been shown to demonstrate increased reliability compared to interviews.(34) Despite these design elements, important limitations remain. We anticipate it will take time for sufficiently large cohorts to accrue prior to adequately powered inferential analyses can be performed. Also, despite efforts to rationalise questionnaire-volumes, it is important to capture the multifaceted contributors and sequelae of gastroduodenal symptoms on patients' lives. Given several different scales are being used, there is a risk of non-response.(31) To mitigate against incomplete data we employ timed reminders, use a patient-friendly app, and have rationalised the questionnaires to minimise questions being asked and maximise relevant outcome data collection.

In conclusion, we present a study protocol for a longitudinal cohort study of patients being investigated with body surface gastric mapping using the Gastric Alimetry™ system. These data will offer insight into the clinical utility and impact of Gastric Alimetry™, a new test to gastroenterology practice, and offer data to explore hypotheses in relation to impact on clinical decisions, treatment responses, and natural histories of disease.

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Figures

Figure 1: Comprehensive overview of data being collected at baseline and each subsequent follow-up.

Figure 2: MyCap mobile application interface for daily symptom ratings. 0-10 Likert scale for stomach burn shown as an example.

Figure 3: Overview of data collection and follow-up

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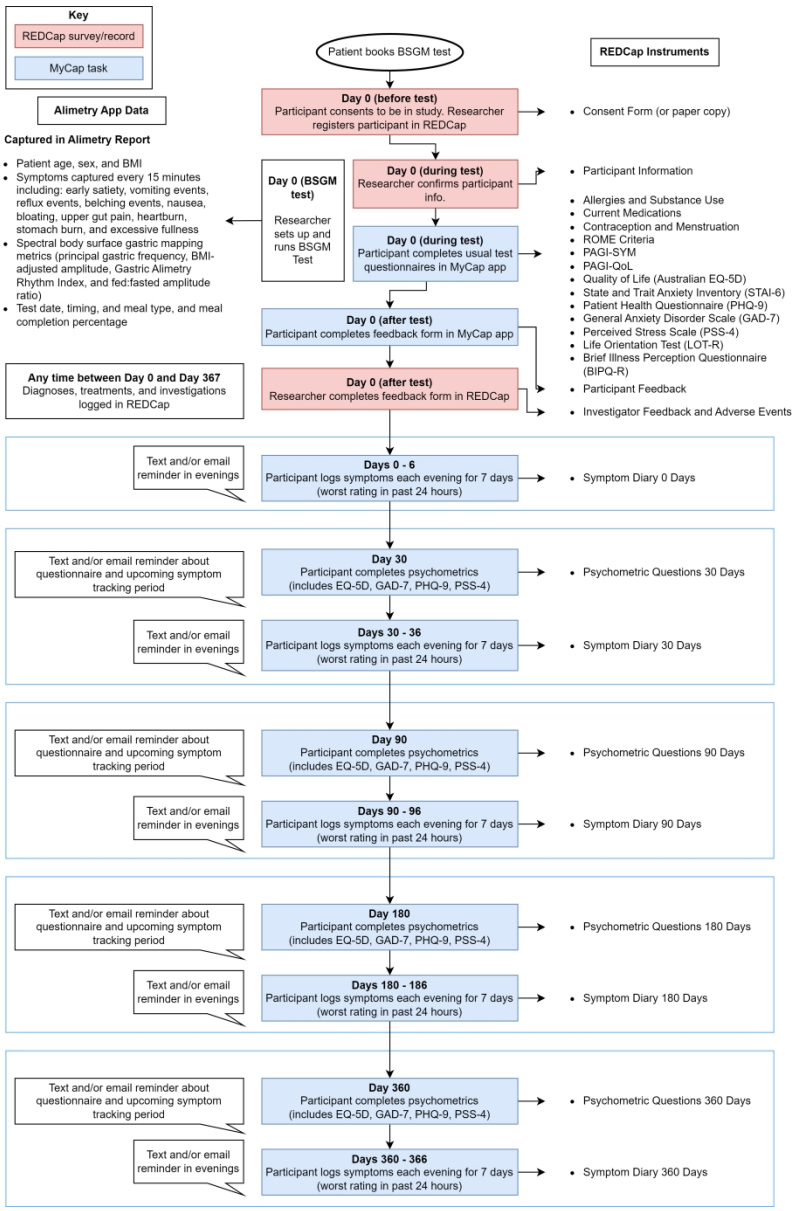

Comprehensive overview of data being collected at baseline and each subsequent follow-up.

596x848mm (157 x 157 DPI)

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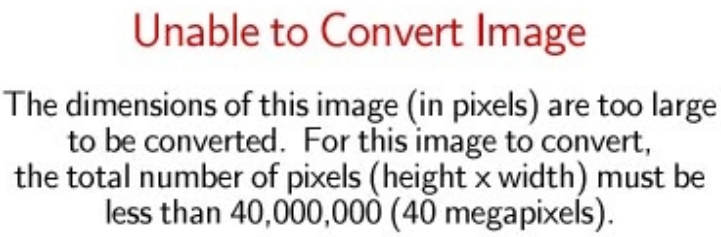

MyCap mobile application interface for daily symptom ratings. 0-10 Likert scale for stomach burn shown as an example.

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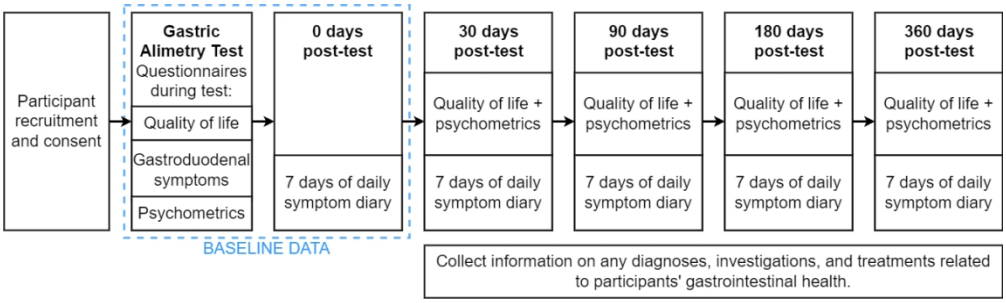

Overview of data collection and follow-up

338x99mm (100 x 100 DPI)

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	1.0
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6-10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6-10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	6
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	6
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5-7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	NA
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Longitudinal outcome monitoring in patients with chronic gastroduodenal symptoms investigated using the Gastric Alimetry™ system: study protocol

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PROTOCOL

Longitudinal outcome monitoring in patients with chronic gastroduodenal symptoms investigated using the Gastric Alimetry™ system: study protocol

Chris Varghese[1], Nicky Dachs[2], Gabriel Schamberg[1,2], Kiel McCool[2], Mikaela Law[1,2], William Xu[1], Stefan Calder[2], Daphne Foong[6], Vincent Ho[6], Charlotte Daker[5], Christopher N. Andrews[4], Armen A Gharibans[1,2,3], Gregory O'Grady[1,2,3]

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Authors' contributions: CV, ND, AG, GOG drafted the manuscript. GS, KM, SC, AG, GOG supervised the protocol design and final manuscript. All authors contributed to the final drafting and review of the manuscript. CV, ND, GS, KM, ML, WX, SC, DF, VH, CD, CAN, AAG, and GO all made substantial contributions to the conception or design of the work; drafting of the work and provided final approval of the version to be published and agreement to be accountable for all aspects of the work.

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Key words: Body surface gastric mapping, gastroenterology, gastroduodenal symptoms, longitudinal outcomes, protocol

Word count: 3405

Data availability: NA

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Abstract

Introduction

The Gastric Alimetry™ platform offers a multimodal assessment of gastric function through body surface gastric mapping (BSGM) and concurrent symptom-tracking via a validated App. We aim to perform a longitudinal cohort study to examine the impact of Gastric Alimetry, and changes in clinical management on patient symptoms, quality of life, and psychological health.

Methods and analysis

This is a prospective multicentre longitudinal observational cohort study of participants with chronic gastroduodenal symptoms. Consecutive participants undergoing Gastric Alimetry™ will be invited to participate. Quality of life will be assessed via EuroQol-5D and the Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL) score. Gastrointestinal symptoms will be assessed via the Patient Assessment of Upper Gastrointestinal Symptom Severity (PAGI-SYM) index, and the Gastroparesis Cardinal Symptom Index (GCSI). Psychometrics will be assessed, including anxiety via the General Anxiety Disorder-7 (GAD-7), perceived stress using the Perceived Stress Scale 4 (PSS-4), and depression via the Patient Health Questionnaire 9 (PHQ-9). Clinical parameters including diagnoses, investigations, and treatments (medication and procedures) will also be captured. Assessments will be made the week after the BSGM test, at 30-days, 90-days, 180-days, and 360-days thereafter. The primary outcome is feasibility of longitudinal follow-up of a cohort that have undergone Gastric Alimetry™ testing; from which patients' continuum of care can be characterised. Secondary outcomes include changes in patient-reported symptoms, quality of life, and psychometrics (anxiety, stress, and depression). Inferential causal analyses will be performed at the within patient-level to explore causal associations between treatment changes and clinical outcomes. The impact of Gastric Alimetry on clinical management will also be captured.

Ethics and dissemination

The protocol has been approved in Aotearoa New Zealand by the Auckland Health Research Ethics Committee (AHREC). Results will be submitted for conference presentation and peer-reviewed publication.

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Registration

Australian New Zealand Clinical Trials Registry (ACTRN12623000443695).

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Introduction

Body surface gastric mapping (BSGM) using the Gastric Alimetry™ System is a breakthrough diagnostic modality for the assessment of gastric function.(1–6) BSGM has found utility in defining underlying aetiologies within a diverse array of cohorts including patients with chronic gastroduodenal symptoms, type 1 diabetes, delayed gastric emptying, and post-gastric surgery.(2,3,7,8) Validated metrics of gastric function and simultaneous symptom-capture is also emerging as a tool to enable clinicians to make decisions based on objective and actionable biomarkers,(9–11) rather than the trial-and-error therapies pervasive in these poorly understood gastroduodenal disorders. In a recent series of patients assumed to have intestinal failure secondary to gut dysmotility, BSGM informed care in 100% of patients, offered an updated diagnosis in 60% and facilitated a cost-saving wean from parenteral nutrition in two thirds of patients.(11)

Longitudinal data capture is required to assess the impact that Gastric Alimtery™ has on long-term care and clinical outcomes. A scalable data platform to rapidly accrue longitudinal data is required to track changes in symptoms, quality of life, and psychological outcomes over time. These data will form the basis of future assessments of treatment decisions at scale. Once such a data platform is established, over time a large repository of longitudinal data will be available to compare the impacts of investigations, medication changes, and procedural interventions on patient outcomes. Such causal inferences can lay the foundation for future randomised trials, with potential to open new avenues for data-driven research within care paradigms in gastroduodenal health.

This manuscript outlines a study protocol for the establishment of a longitudinal data capture system in this context, including a) data and outcomes being collected, time course of collection, and rationale; b) a detailed overview of data linkage strategies that enable multimodal and ongoing data capture; and c) data management and infrastructure to facilitate ongoing analytics.

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Methods

This protocol is described in accordance to the relevant items of the SPIRIT checklist (Standard Protocol items: Recommendations for Interventional Trials).(12) The protocol has been approved in Aotearoa New Zealand by the Auckland Health Research Ethics Committee (AHREC).

Study objectives

At the time of the initial Gastric Alimetry™ test, comprehensive gastrointestinal disorder, quality of life, and psychometrics assessments will be completed. This study aims to follow up all consenting participants undergoing Gastric Alimetry™ testing over a period of one year to assess changes in self-reported symptoms, quality of life, anxiety, stress, and depression measures, and changes in clinical care (including investigations initiated after Gastric Alimetry™ testing, and treatments started or changed). We aim to generate a database of patients to assess within-subject changes with regards to relevant clinical management initiated on the basis of Gastric Alimetry™ in patients with chronic gastroduodenal symptoms.

Specific clinical questions sought to be answered through this process include:

1) Define the natural history of chronic gastroduodenal disorders (including Rome-IV defined functional dyspepsia, chronic nausea and vomiting syndrome, and gastroparesis defined based on gastric emptying testing) by quantifying changes in symptoms, quality of life, and health psychometrics over a 1-year period
2) Define the natural history with regards to symptoms, quality of life, and health psychometrics stratified by Gastric Alimetry phenotypes (as described by O'Grady et al.)(13), initially with comparison to the current diagnostic paradigm (i.e., via Rome-IV and gastric emptying testing)
3) Quantify healthcare utilisation over a 1-year period among patients with chronic gastroduodenal disorders (namely, investigations, changes in pharmacological management, referrals to other services, and procedural interventions including endoscopic and surgical)
4) Comparison of longitudinal outcomes among patients with gastroparesis treated with G-POEM as a standalone cohort, and in comparison to matched patients with gastroparesis that do not undergo G-POEM

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Moreover, this protocol describes the development of a database platform which will enable investigation of further hypotheses relevant to chronic gastroduodenal disorders.

Study design

This is a prospective, multicentre, longitudinal, observational cohort study that will occur via the BSGM Consortium (an international network of collaborators performing Gastric Alimetry™ tests). Auckland, New Zealand will be the lead site; other recruiting centres at this stage include Calgary, Canada; and Western Sydney, Australia. Further sites are eligible to enrol at any time.

Study setting

Any site performing Gastric Alimetry™ tests is eligible to participate. Each site uses a standardised Gastric Alimetry™ App through which patient-level expressions of interest will be obtained. Thereafter, interested participants will be registered onto the REDCap system, where informed digital consent for participation will be sought, after which standardised study questionnaires will be administered. Participants will receive surveys via MyCap, a participant-facing app linked with REDCap.

Study procedures

Test procedures

The Gastric Alimetry test has been described in detail elsewhere.(1,2,5,13) However, in brief: The system comprises a stretchable array (8x8 electrodes + 2 reference electrodes; 2 cm spacing; Ag/AgCl contacts with hydrogel coating), a portable data logger to enable signal capture, and a symptom-logging iPad App which is time-synchronised to the data logger by Bluetooth (**Figure 1A**). The standardised test involving 30 minutes of fasting baseline, consumption of a standard test-meal, and 4.5-hour postprandial recording (**Figure 1B**). During the test participants sit reclined limiting movements. Subjects fast for a minimum of 8-hours and avoid medications affecting motility 48-hours prior to testing. The array is placed over the epigastrium (capturing the stomach in >99% of subjects). The electrophysiological signal is further optimised with removal of excess hair and skin-prep (NuPrep™, Weaver, CO) to reduce impedance, and an automated artifact rejection pipeline (**Figure**

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1C).(14) During the test, the symptoms of epigastric pain, epigastric fullness, early satiety, epigastric burning, heartburn, and nausea, are assessed on 0-10 numeric rating scales at 15-minute intervals, and vomiting, reflux, and belching are captured as discrete events, using a validated pictograms-based approach (**Figure 1A**).(6)

Test outputs:

Gastric Alimetry test outputs are comprehensively overviewed in a recent technical review.(13) In brief, 3 main outputs are generated (**Figure 1C**):

a) Spectral outputs: these include the BMI-adjusted amplitude, Principle Gastric Frequency, fed:fasted amplitude ratio, and the Gastric Alimetry Rhythm Index. Further details toward the development, validation, and interpretation can be found in the following references (5,13,15).
b) Spatial outputs: these are currently under development, but preliminary work toward direction of propagation when coordinated gastric activity exists is possible (see (1,7).
c) Symptom outputs: novel measures of symptom severity in relation to the gastric amplitude curve have recently been developed. In particular the correlation, or lack thereof between symptom severity curves, and gastric amplitude curves offer insights toward their aetiological basis (see (16,17)).

Sample size and power calculation

The broader aim of this study is to develop a database of participants with chronic gastroduodenal symptoms that follow a range of real-world clinical management pathways. Formal evaluations of causal links between clinical diagnoses, investigations, and management to changes in patient-reported symptoms, quality of life, and psychometrics will ultimately require randomised controlled trials. However, data accrued from this longitudinal follow-up will inform power calculations for subsequent pre-specified research questions. Thereafter, further data collection is expected, with large-scale expansion to power further analytics. Sample size calculations will be performed prior to each specific analysis, to ensure adequate power toward specific hypothesis being investigated; where mixed models will be employed, sample size calculations will account for cluster sampling.

Data collection and management

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All data will be collected prospectively and stored online in an encrypted format through a secure Research Electronic Data Capture (REDCap) web server hosted by the University of Auckland.(18). Initial and all subsequent surveys will be administered using MyCap, a participant-facing mobile application integrated with REDCap.(19).

Eligibility criteria

All adults aged 18 years and above consenting to a Gastric Alimetry™ test are eligible for inclusion. The primary cohort of interest are those meeting Rome-IV criteria for chronic gastroduodenal disorders (including functional dyspepsia, chronic nausea and vomiting syndromes, cannabinoid hyperemesis syndrome, and cyclical vomiting syndrome) and/or gastroparesis, defined by retention of >10% of intraluminal content after 4 hours during a gastric emptying test. Given this protocol may be translatable across domains, specific cohorts including post-surgical patients (e.g., after gastric surgery) may also be recruited to enable longitudinal follow-up and symptom monitoring of this cohort. Exclusion criteria include age <18 years, history of skin allergies or a history of extreme sensitivity to cosmetics or lotions, and vulnerable groups such as prisoners, individuals known to have cognitive impairment or institutionalised individuals. No exclusions will be made based on the clinical management of patients as, for each intervention, a series of 'exposed' and 'controlled' participants will be required to assess causal relationships. Healthy volunteers that consent can also be included to form a comparator arm for analyses.

Participant informed consent process

All individuals undergoing a Gastric Alimetry™ test will be invited to participate in the study via the Gastric Alimetry™ App. Those who express interest will be loaded onto the REDCap system and will receive a REDCap-initiated digital consent form. Those who provide informed consent via an e-signature will be loaded into MyCap, enrolled into the study, and issued a unique study identification number within REDCap that is linked to their MyCap and Gastric Alimetry™ records.

Outcomes

Quality of life will be assessed via EuroQol-5D (EQ-5D) and the Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL) score. Gastrointestinal symptoms will be

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assessed via the Patient Assessment of Upper Gastrointestinal Symptom Severity (PAGI-SYM) index, and the Gastroparesis Cardinal Symptom Index (GCSI). Anxiety will be assessed through the General Anxiety Disorder-7 (GAD-7),(20) perceived stress using the Perceived Stress Scale 4 (PSS-4),(21) and depression via the Patient Health Questionnaire 9 (PHQ-9).(20) Clinical parameters including, diagnoses (Gastric Alimetry™ phenotype, Rome-IV diagnosis),(13) investigations (gastric emptying, transit studies, manometry, endoscopy), and treatments (medications, and procedures), as well as changes in the above measures, and date of change will also be captured. A comprehensive overview of the data being collected at each time point is overviewed in **Figure 2**.

Gastrointestinal symptoms

At each of the post-test time points (index test, 30-days, 90-days, 180-days and 365-days), participants will be asked to complete a daily symptom diary for seven days. Each evening, they will rate the severity of seven gastrointestinal symptoms over the past 24 hours. Each symptom is rated using a 0–10 Likert scale, with anchors at 0 “none,” indicating no symptom experience, and 10 indicating the “most severe imaginable” extent of a symptom experience. The rating is determined by the worst symptom experience in the past 24 hours for each symptom. The symptoms are stomach burn, stomach pain, nausea, bloating, postprandial fullness, early satiation, belching, and number of vomiting events. An additional rating distress arising from excessive belching is included, using a 0-10 Likert scale, with anchors at 0 “none,” and 10 “worst imaginable bother.” **Figure 3** shows an example of the MyCap interface for symptom ratings.

This symptom questionnaire is adapted from the basis the Functional Dyspepsia Symptom Diary (FDSD) and follows the recommended 24-hour recall period to minimise recall bias and account for day-to-day variation.(22) The questionnaire follows similar principles to the The American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index Daily Diary (ANMS GCSI-DD), which recommends using one-week blocks for baseline and follow-up symptom scoring and completion of the diary at the same time each evening, prior to bedtime, to capture the patient’s experience after all of the day’s meals.(23)

Psychometric and Quality of Life Questionnaires

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During the index Gastric Alimetry™ test, participants will complete the EQ-5D and PAGI-QOL questionnaire, and at each follow-up time point, the EQ-5D will be completed. The EQ-5D, a questionnaire on health-related quality of life, was chosen for its wide acceptance, brevity, and advantages for cost-utility analyses.(24,25) To quantitatively assess self-reported anxiety, stress, and depression symptomatology, widely validated and accepted psychometric tools will be administered, including the GAD-7,(20) PSS-4,(21) and PHQ-9 respectively.(20) These will be administered once per time point, unlike the repeating symptom diaries.

Clinical management / interventions

The following investigations, clinical management decisions, and treatments will be captured to facilitate observational analyses of causal hypotheses.

- Gastric Alimetry results (spectral metrics,(5) spatial metrics, patient phenotype – defined elsewhere (13))
- Investigations
    - Imaging: X-ray, ultrasound, computed tomography scans, magnetic resonance imaging, vascular imaging, BSGM, scintigraphy, antro-duodenal manometry
    - Specialised blood tests: coeliac serology, H pylori stool PCR, alpha-1-antitrypsin, ceruloplasmin, liver function tests, IgA, lactose tolerance test, thyroid function tests
    - Endoscopy: esophagogastroduodenoscopy +/- biopsy
- Referrals
    - Specialist or referral to another service (e.g., psychiatry, surgery, endocrinology etc.)
- Treatments
    - Non-pharmacological: lifestyle modifications (e.g., initiating an exercise program), change in diet, counselling (in-person, virtual, app-based), psychotherapy (e.g. cognitive behavioural therapy, acceptance commitment therapy, mindfulness, hypnosis, relaxation therapy; in-person, virtual, app-based)
    - Medications: neuromodulator, prokinetic, antiemetic, anxiolytic, PPI, H2-receptor antagonist, other
    - Endoscopic procedures: gastric peroral endoscopic myotomy (G-POEM), pyloric botox

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- Surgery: anti-reflux surgery, gastrointestinal resection, small intestinal diversion

Follow-up

Immediately following the Gastric Alimetry™ test, participants will complete a daily symptom diary each evening for seven-days. At 30-days post-test, participants will complete a combined psychometric and quality of life questionnaire, followed by seven days of daily symptom diaries. This combination of psychometrics, quality of life, and symptom questionnaires will repeat at 90 days, 180 days, and 360 days (**Figure 4**). The MyCap system will remain open for patients to enter changes in diagnosis or management in consultation with their clinical care team (including the research team at the discretion of the recruiting sites).

To encourage engagement, participants will be able to use their own mobile phones to access MyCap's patient-centred interface. To facilitate successful follow-up and data completeness participants will be sent scheduled text message or email reminders to complete questionnaires using Twilio, a third-party REDCap add-on. Twilio is a messaging platform that allows SMS messages to be programmatically scheduled and sent worldwide.(26) Questionnaire timing will be scheduled based on individual patient timelines, customised using the date of initial Gastric Alimetry™ test.

Statistical analysis

This protocol describes the development of a standardised and scalable data platform for tracking changes in symptoms, quality of life, and psychological outcomes over time. Exploratory and pilot analyses will be performed within acknowledged limitations of a non-randomised study design. Longitudinal assessments allow for the evaluation of the efficacy and utility of diagnostic assessments and treatments offered to patients. Monitoring within-subject changes has been shown to offer advantages in establishing causal relationships.(27) As data accrues over time, a large repository of longitudinal data will be available to compare the impacts of investigations, medication changes, and procedural interventions on patient-reported outcomes. Such causal inferences can lay the foundation for future randomised trials, informing power calculations, and identifying research priorities.

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Preliminary analyses will include descriptive comparative statistics, such as univariate between-group comparisons and also before-after testing (using individuals as their own control), where pre- and post-intervention paired statistics will be employed. Normally distributed data will be reported as mean (SD), and non-normally distributed data as median (IQR). Statistical comparisons will be performed using independent samples t-tests, analysis of variance (ANOVA), paired-samples t tests, or repeated measures ANOVA for normally distributed variables; Mann-Whitney U, Kruskal-Wallis tests, Wilcoxon signed-rank test, or Friedman's test for non-normally distributed continuous or ordinal variables; and $\chi 2$ tests or McNemar's test for categorical variables. Regression models will be used as appropriate for relevant outcomes including multivariate linear regression with adjustment for relevant demographic confounders. If sample sizes allow, mixed effects hierarchical models will be employed to account for natural clustering structures e.g., at the centre-level. Interclass correlations will be assessed via the interclass correlation coefficient. Model selection will be guided by parsimony, clinically plausible relationships between predictors and outcomes, and minimisation of the Akaike information criterion.(28) Missing data will be interrogated to assess if they are missing at random, and multiple imputation by chained equations or pairwise deletion will be employed as appropriate.

Study delivery and quality assurance

This longitudinal cohort study will be centrally managed by a steering group consisting of expert statisticians, data managers, and clinician scientists with oversight and guidance from key opinion leaders in the field of gastroenterology and gastrointestinal surgery. Regular data-auditing will be performed with communication between the steering group and individual sites. Training resources are available to ensure standardised use of the Gastric Alimetry™ system for all device users.(29)

Patient and public involvement

Several rounds of patient interviews were completed during the development stage of the Gastric Alimetry™ platform,(6,30) which informed the design and delivery of the app. Patient feedback will be actively sought at the time of each test and will contribute to ongoing development and data applications. Interviews with a range of patients, and gastric disorder patient advocacy group leaders have informed relevant study designs and key clinical questions; most relevant to this protocol being

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the impact on individual patient's continuum of care to reduce investigations, offer more actionable diagnoses, relationships to psychological health variables, and to direct more efficacious therapies.

Ethics and dissemination

Ethics approvals have been sought according to the requirements of each participating centre. At the lead site, the protocol has been approved in Aotearoa New Zealand by the Auckland Health Research Ethics Committee (AHREC; ref AH1130). Results will be submitted for conference presentations and peer-reviewed publication.

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Discussion

Gastric Alimetry™ is emerging as a significant new clinical test of gastric function combining gastric electrophysiology and concurrent symptom tracking.(1,6) This diagnostic tool offers a new paradigm for the investigation and management of patients with chronic gastroduodenal disorders,(28) but longitudinal data on outcomes is now required to define its impact on clinical workflows, diagnoses, and outcomes. Here we present a longitudinal cohort study protocol to assess the impact of Gastric Alimetry™ on patients' continuum of care; this will offer robust data for assessing relationships between clinical diagnoses, and management decisions on patients' symptoms, psychological symptomatology, and quality of life. These observational data will guide hypothesis testing, facilitating prioritisation and powering of future trials to advance the field.

This study also aims to generate evidence in support of putative mechanisms for poorly understood gastroduodenal symptoms in line with Tack et al's plausibility criteria for disease mechanisms in functional gastrointestinal disorders.(31) The longitudinal study design in particular is essential to generate evidence for the fifth putative criterion within this framework: 'Therapeutic response'/'Congruent natural history', which states that treatment aimed at correcting an underlying disorder improves symptoms, or, changes in symptom severity parallel changes in the severity of the disturbance.(31) This evaluations are also in-line with innovation frameworks which recommend large-scale longitudinal surveillance of outcomes when novel medical innovations such as the Gastric Alimetry™ system are employed in routine clinical use.(32,33)

We developed an integrated digital platform for robust data-linkage, accurate, and secure storage of longitudinal, repeated measures data. REDCap serves as the secure data storage infrastructure with the mobile MyCap app being the patient-facing platform for collecting patient-reported outcomes. Data completeness is encouraged through the use of Twilio, enabling automated, scheduled reminders. Scheduled tasks personalised to each individual patients' timelines facilitate scalability to a large volume of patients.(34) These data are then linked to gastric electrophysiological signal data after refined artefact rejection and algorithmic post-processing,(31) and the Gastric Alimetry™ App data which are stored on a HIPAA-compliant cloud platform.(35)

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Strengths and limitations

This study utilises validated, widely used instruments to measure self-reported gastrointestinal symptoms, quality of life, and psychological factors. Validated questionnaires were chosen for their external validity, brevity so as to be pragmatic with data collection, and reduced burden on patients. The use of self-administered questionnaires and diaries have also been shown to demonstrate increased reliability compared to interviews.(36) Despite these design elements, important limitations remain. We anticipate it will take time for sufficiently large cohorts to accrue prior to adequately powered inferential analyses can be performed. Also, despite efforts to rationalise questionnaire-volumes, it is important to capture the multifaceted contributors and sequelae of gastroduodenal symptoms on patients' lives. Given several different scales are being used, there is a risk of non-response.(34) To mitigate against incomplete data we employ timed reminders, use a patient-friendly app, and have rationalised the questionnaires to minimise questions being asked and maximise relevant outcome data collection. A 1-year follow-up was determined to be the most pragmatic for the majority of hypotheses aimed to be addressed using this protocol, however, in specific cases, longer follow-up than 1-year may be desirable, and as such the system described here remains flexible to such alterations.

In conclusion, we present a study protocol for a longitudinal cohort study of patients being investigated with body surface gastric mapping using the Gastric Alimetry™ system. These data will offer insight into the clinical utility and impact of Gastric Alimetry™, a new test to gastroenterology practice, and offer data to explore hypotheses in relation to impact on clinical decisions, treatment responses, and natural histories of disease.

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Figures

Figure 1: Overview of the Gastric Alimetry system and analysis pipeline. A) Gastric Alimetry system and App; B) Gastric Alimetry test procedure; C) Signal processing pipeline and end outputs.

Figure 2: Comprehensive overview of data being collected at baseline and each subsequent follow-up.

Figure 3: MyCap mobile application interface for daily symptom ratings. 0-10 Likert scale for stomach burn shown as an example.

Figure 4: Overview of data collection and follow-up

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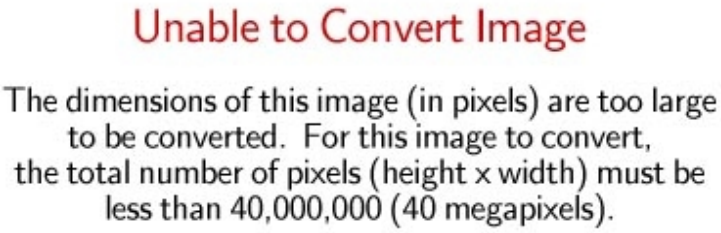

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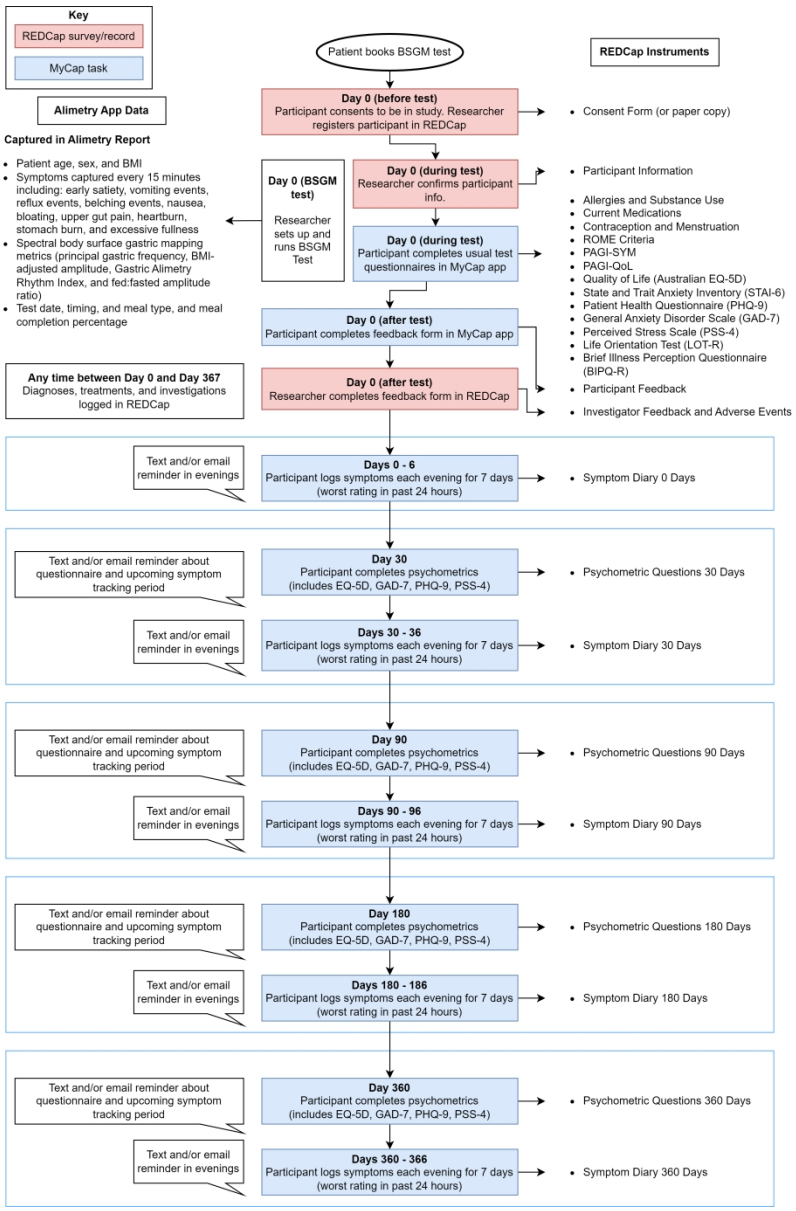

Figure 2: Comprehensive overview of data being collected at baseline and each subsequent follow-up.

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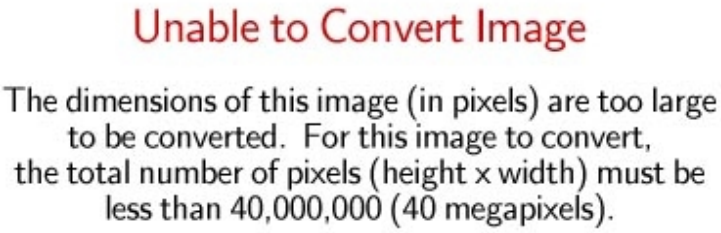

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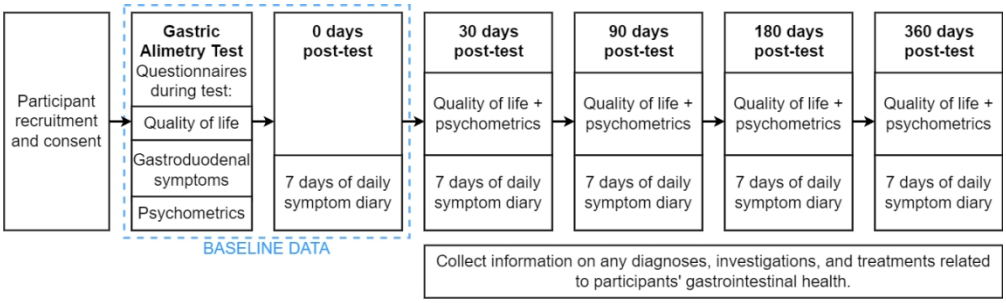

Figure 4: Overview of data collection and follow-up

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	1.0
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6-10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6-10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	6
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	6
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5-7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	NA
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Longitudinal outcome monitoring in patients with chronic gastroduodenal symptoms investigated using the Gastric Alimetry™ system: study protocol

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PROTOCOL

Longitudinal outcome monitoring in patients with chronic gastroduodenal symptoms investigated using the Gastric Alimetry™ system: study protocol

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Authors' contributions: CV, ND, AG, GOG drafted the manuscript. GS, KM, SC, AG, GOG supervised the protocol design and final manuscript. All authors contributed to the final drafting and review of the manuscript. CV, ND, GS, KM, ML, WX, SC, DF, VH, CD, CAN, AAG, and GO all made substantial contributions to the conception or design of the work; drafting of the work and provided final approval of the version to be published and agreement to be accountable for all aspects of the work.

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Abstract

Introduction

The Gastric Alimetry™ platform offers a multimodal assessment of gastric function through body surface gastric mapping (BSGM) and concurrent symptom-tracking via a validated App. We aim to perform a longitudinal cohort study to examine the impact of Gastric Alimetry, and changes in clinical management on patient symptoms, quality of life, and psychological health.

Methods and analysis

This is a prospective multicentre longitudinal observational cohort study of participants with chronic gastroduodenal symptoms. Consecutive participants undergoing Gastric Alimetry™ will be invited to participate. Quality of life will be assessed via EuroQol-5D and the Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL) score. Gastrointestinal symptoms will be assessed via the Patient Assessment of Upper Gastrointestinal Symptom Severity (PAGI-SYM) index, and the Gastroparesis Cardinal Symptom Index (GCSI). Psychometrics will be assessed, including anxiety via the General Anxiety Disorder-7 (GAD-7), perceived stress using the Perceived Stress Scale 4 (PSS-4), and depression via the Patient Health Questionnaire 9 (PHQ-9). Clinical parameters including diagnoses, investigations, and treatments (medication and procedures) will also be captured. Assessments will be made the week after the BSGM test, at 30-days, 90-days, 180-days, and 360-days thereafter. The primary outcome is feasibility of longitudinal follow-up of a cohort that have undergone Gastric Alimetry™ testing; from which patients' continuum of care can be characterised. Secondary outcomes include changes in patient-reported symptoms, quality of life, and psychometrics (anxiety, stress, and depression). Inferential causal analyses will be performed at the within patient-level to explore causal associations between treatment changes and clinical outcomes. The impact of Gastric Alimetry on clinical management will also be captured.

Ethics and dissemination

The protocol has been approved in Aotearoa New Zealand by the Auckland Health Research Ethics Committee (AHREC). Results will be submitted for conference presentation and peer-reviewed publication.

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Registration

Australian New Zealand Clinical Trials Registry (ACTRN12623000443695).

Strengths and limitations of this study

- This is a prospective, multicentre study, which will capture a wide range of management outcomes over a 1-year period in chronic gastroduodenal disorders
- Integration of a patient-facing MyCap system aims to maximise successful follow up and data accuracy
- This study is an observational study without prespecified randomisation
- This is a protocol for a longitudinal follow-up platform and therefore dedicated studies will need to define prespecified hypotheses, and power calculations accordingly

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Introduction

Body surface gastric mapping (BSGM) using the Gastric Alimetry™ System is a breakthrough diagnostic modality for the assessment of gastric function.[1–6] BSGM has found utility in defining underlying aetiologies within a diverse array of cohorts including patients with chronic gastroduodenal symptoms, type 1 diabetes, delayed gastric emptying, and post-gastric surgery.[2,3,7,8] Validated metrics of gastric function and simultaneous symptom-capture is also emerging as a tool to enable clinicians to make decisions based on objective and actionable biomarkers,[9–11] rather than the trial-and-error therapies pervasive in these poorly understood gastroduodenal disorders. In a recent series of patients assumed to have intestinal failure secondary to gut dysmotility, BSGM informed care in 100% of patients, offered an updated diagnosis in 60% and facilitated a cost-saving wean from parenteral nutrition in two thirds of patients.[11]

Longitudinal data capture is required to assess the impact that Gastric Alimtery™ has on long-term care and clinical outcomes. A scalable data platform to rapidly accrue longitudinal data is required to track changes in symptoms, quality of life, and psychological outcomes over time. These data will form the basis of future assessments of treatment decisions at scale. Once such a data platform is established, over time a large repository of longitudinal data will be available to compare the impacts of investigations, medication changes, and procedural interventions on patient outcomes. Such causal inferences can lay the foundation for future randomised trials, with potential to open new avenues for data-driven research within care paradigms in gastroduodenal health.

This manuscript outlines a study protocol for the establishment of a longitudinal data capture system in this context, including a) data and outcomes being collected, time course of collection, and rationale; b) a detailed overview of data linkage strategies that enable multimodal and ongoing data capture; and c) data management and infrastructure to facilitate ongoing analytics.

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Methods

This protocol is described in accordance to the relevant items of the SPIRIT checklist (Standard Protocol items: Recommendations for Interventional Trials).[12] The protocol has been approved in Aotearoa New Zealand by the Auckland Health Research Ethics Committee (AHREC).

Study objectives

At the time of the initial Gastric Alimetry™ test, comprehensive gastrointestinal disorder, quality of life, and psychometrics assessments will be completed. This study aims to follow up all consenting participants undergoing Gastric Alimetry™ testing over a period of one year to assess changes in self-reported symptoms, quality of life, anxiety, stress, and depression measures, and changes in clinical care (including investigations initiated after Gastric Alimetry™ testing, and treatments started or changed). We aim to generate a database of patients to assess within-subject changes with regards to relevant clinical management initiated on the basis of Gastric Alimetry™ in patients with chronic gastroduodenal symptoms.

Specific clinical questions sought to be answered through this process include:

1) Define the natural history of chronic gastroduodenal disorders (including Rome-IV defined functional dyspepsia, chronic nausea and vomiting syndrome, and gastroparesis defined based on gastric emptying testing) by quantifying changes in symptoms, quality of life, and health psychometrics over a 1-year period
2) Define the natural history with regards to symptoms, quality of life, and health psychometrics stratified by Gastric Alimetry phenotypes (as described by O'Grady et al.)[13], initially with comparison to the current diagnostic paradigm (i.e., via Rome-IV and gastric emptying testing)
3) Quantify healthcare utilisation over a 1-year period among patients with chronic gastroduodenal disorders (namely, investigations, changes in pharmacological management, referrals to other services, and procedural interventions including endoscopic and surgical)
4) Comparison of longitudinal outcomes among patients with gastroparesis treated with G-POEM as a standalone cohort, and in comparison to matched patients with gastroparesis that do not undergo G-POEM

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Moreover, this protocol describes the development of a database platform which will enable investigation of further hypotheses relevant to chronic gastroduodenal disorders.

Study design

This is a prospective, multicentre, longitudinal, observational cohort study that will occur via the BSGM Consortium (an international network of collaborators performing Gastric Alimetry™ tests). Auckland, New Zealand will be the lead site; other recruiting centres at this stage include Calgary, Canada; and Western Sydney, Australia. Further sites are eligible to enrol at any time.

Study setting

Any site performing Gastric Alimetry™ tests is eligible to participate. Each site uses a standardised Gastric Alimetry™ App through which patient-level expressions of interest will be obtained. Thereafter, interested participants will be registered onto the REDCap system, where informed digital consent for participation will be sought, after which standardised study questionnaires will be administered. Participants will receive surveys via MyCap, a participant-facing app linked with REDCap.

Study procedures

Test procedures

The Gastric Alimetry test has been described in detail elsewhere.[1,2,5,13] However, in brief: The system comprises a stretchable array (8x8 electrodes + 2 reference electrodes; 2 cm spacing; Ag/AgCl contacts with hydrogel coating), a portable data logger to enable signal capture, and a symptom-logging iPad App which is time-synchronised to the data logger by Bluetooth (**Figure 1A**). The standardised test involving 30 minutes of fasting baseline, consumption of a standard test-meal, and 4.5-hour postprandial recording (**Figure 1B**). During the test participants sit reclined limiting movements. Subjects fast for a minimum of 8-hours and avoid medications affecting motility 48-hours prior to testing. The array is placed over the epigastrium (capturing the stomach in >99% of subjects). The electrophysiological signal is further optimised with removal of excess hair and skin-prep (NuPrep™, Weaver, CO) to reduce impedance, and an automated artifact rejection pipeline (**Figure**

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1C).[14] During the test, the symptoms of epigastric pain, epigastric fullness, early satiety, epigastric burning, heartburn, and nausea, are assessed on 0-10 numeric rating scales at 15-minute intervals, and vomiting, reflux, and belching are captured as discrete events, using a validated pictograms-based approach (**Figure 1A**).[6]

Test outputs:

Gastric Alimetry test outputs are comprehensively overviewed in a recent technical review.[13] In brief, 3 main outputs are generated (**Figure 1C**):

a) Spectral outputs: these include the BMI-adjusted amplitude, Principle Gastric Frequency, fed:fasted amplitude ratio, and the Gastric Alimetry Rhythm Index. Further details toward the development, validation, and interpretation can be found in the following references [5,13,15].
b) Spatial outputs: these are currently under development, but preliminary work toward direction of propagation when coordinated gastric activity exists is possible (see [1,7].
c) Symptom outputs: novel measures of symptom severity in relation to the gastric amplitude curve have recently been developed. In particular the correlation, or lack thereof between symptom severity curves, and gastric amplitude curves offer insights toward their aetiological basis (see [16,17]).

Sample size and power calculation

The broader aim of this study is to develop a database of participants with chronic gastroduodenal symptoms that follow a range of real-world clinical management pathways. Formal evaluations of causal links between clinical diagnoses, investigations, and management to changes in patient-reported symptoms, quality of life, and psychometrics will ultimately require randomised controlled trials. However, data accrued from this longitudinal follow-up will inform power calculations for subsequent pre-specified research questions. Thereafter, further data collection is expected, with large-scale expansion to power further analytics. Sample size calculations will be performed prior to each specific analysis, to ensure adequate power toward specific hypothesis being investigated; where mixed models will be employed, sample size calculations will account for cluster sampling.

Data collection and management

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All data will be collected prospectively and stored online in an encrypted format through a secure Research Electronic Data Capture (REDCap) web server hosted by the University of Auckland.[18]. Initial and all subsequent surveys will be administered using MyCap, a participant-facing mobile application integrated with REDCap.[19].

Eligibility criteria

All adults aged 18 years and above consenting to a Gastric Alimetry™ test are eligible for inclusion. The primary cohort of interest are those meeting Rome-IV criteria for chronic gastroduodenal disorders (including functional dyspepsia, chronic nausea and vomiting syndromes, cannabinoid hyperemesis syndrome, and cyclical vomiting syndrome) and/or gastroparesis, defined by retention of >10% of intraluminal content after 4 hours during a gastric emptying test. Given this protocol may be translatable across domains, specific cohorts including post-surgical patients (e.g., after gastric surgery) may also be recruited to enable longitudinal follow-up and symptom monitoring of this cohort. Exclusion criteria include age <18 years, history of skin allergies or a history of extreme sensitivity to cosmetics or lotions, and vulnerable groups such as prisoners, individuals known to have cognitive impairment or institutionalised individuals. No exclusions will be made based on the clinical management of patients as, for each intervention, a series of 'exposed' and 'controlled' participants will be required to assess causal relationships. Healthy volunteers that consent can also be included to form a comparator arm for analyses.

Participant informed consent process

All individuals undergoing a Gastric Alimetry™ test will be invited to participate in the study via the Gastric Alimetry™ App. Those who express interest will be loaded onto the REDCap system and will receive a REDCap-initiated digital consent form. Those who provide informed consent via an e-signature will be loaded into MyCap, enrolled into the study, and issued a unique study identification number within REDCap that is linked to their MyCap and Gastric Alimetry™ records.

Outcomes

Quality of life will be assessed via EuroQol-5D (EQ-5D) and the Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL) score. Gastrointestinal symptoms will be

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assessed via the Patient Assessment of Upper Gastrointestinal Symptom Severity (PAGI-SYM) index, and the Gastroparesis Cardinal Symptom Index (GCSI). Anxiety will be assessed through the General Anxiety Disorder-7 (GAD-7),[20] perceived stress using the Perceived Stress Scale 4 (PSS-4),[21] and depression via the Patient Health Questionnaire 9 (PHQ-9).[20] Clinical parameters including, diagnoses (Gastric Alimetry™ phenotype, Rome-IV diagnosis),[13] investigations (gastric emptying, transit studies, manometry, endoscopy), and treatments (medications, and procedures), as well as changes in the above measures, and date of change will also be captured. A comprehensive overview of the data being collected at each time point is overviewed in **Figure 2**.

Gastrointestinal symptoms

At each of the post-test time points (index test, 30-days, 90-days, 180-days and 365-days), participants will be asked to complete a daily symptom diary for seven days. Each evening, they will rate the severity of seven gastrointestinal symptoms over the past 24 hours. Each symptom is rated using a 0–10 Likert scale, with anchors at 0 “none,” indicating no symptom experience, and 10 indicating the “most severe imaginable” extent of a symptom experience. The rating is determined by the worst symptom experience in the past 24 hours for each symptom. The symptoms are stomach burn, stomach pain, nausea, bloating, postprandial fullness, early satiation, belching, and number of vomiting events. An additional rating distress arising from excessive belching is included, using a 0-10 Likert scale, with anchors at 0 “none,” and 10 “worst imaginable bother.” **Figure 3** shows an example of the MyCap interface for symptom ratings.

This symptom questionnaire is adapted from the basis the Functional Dyspepsia Symptom Diary (FDSD) and follows the recommended 24-hour recall period to minimise recall bias and account for day-to-day variation.[22] The questionnaire follows similar principles to the The American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index Daily Diary (ANMS GCSI-DD), which recommends using one-week blocks for baseline and follow-up symptom scoring and completion of the diary at the same time each evening, prior to bedtime, to capture the patient’s experience after all of the day’s meals.[23]

Psychometric and Quality of Life Questionnaires

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During the index Gastric Alimetry™ test, participants will complete the EQ-5D and PAGI-QOL questionnaire, and at each follow-up time point, the EQ-5D will be completed. The EQ-5D, a questionnaire on health-related quality of life, was chosen for its wide acceptance, brevity, and advantages for cost-utility analyses.[24,25] To quantitatively assess self-reported anxiety, stress, and depression symptomatology, widely validated and accepted psychometric tools will be administered, including the GAD-7,[20] PSS-4,[21] and PHQ-9 respectively.[20] These will be administered once per time point, unlike the repeating symptom diaries.

Clinical management / interventions

The following investigations, clinical management decisions, and treatments will be captured to facilitate observational analyses of causal hypotheses.

- Gastric Alimetry results (spectral metrics,[5] spatial metrics, patient phenotype – defined elsewhere [13])
- Investigations
    - Imaging: X-ray, ultrasound, computed tomography scans, magnetic resonance imaging, vascular imaging, BSGM, scintigraphy, antro-duodenal manometry
    - Specialised blood tests: coeliac serology, H pylori stool PCR, alpha-1-antitrypsin, ceruloplasmin, liver function tests, IgA, lactose tolerance test, thyroid function tests
    - Endoscopy: esophagogastroduodenoscopy +/- biopsy
- Referrals
    - Specialist or referral to another service (e.g., psychiatry, surgery, endocrinology etc.)
- Treatments
    - Non-pharmacological: lifestyle modifications (e.g., initiating an exercise program), change in diet, counselling (in-person, virtual, app-based), psychotherapy (e.g. cognitive behavioural therapy, acceptance commitment therapy, mindfulness, hypnosis, relaxation therapy; in-person, virtual, app-based)
    - Medications: neuromodulator, prokinetic, antiemetic, anxiolytic, PPI, H2-receptor antagonist, other
    - Endoscopic procedures: gastric peroral endoscopic myotomy (G-POEM), pyloric botox

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- Surgery: anti-reflux surgery, gastrointestinal resection, small intestinal diversion

Follow-up

Immediately following the Gastric Alimetry™ test, participants will complete a daily symptom diary each evening for seven-days. At 30-days post-test, participants will complete a combined psychometric and quality of life questionnaire, followed by seven days of daily symptom diaries. This combination of psychometrics, quality of life, and symptom questionnaires will repeat at 90 days, 180 days, and 360 days (**Figure 4**). The MyCap system will remain open for patients to enter changes in diagnosis or management in consultation with their clinical care team (including the research team at the discretion of the recruiting sites).

To encourage engagement, participants will be able to use their own mobile phones to access MyCap's patient-centred interface. To facilitate successful follow-up and data completeness participants will be sent scheduled text message or email reminders to complete questionnaires using Twilio, a third-party REDCap add-on. Twilio is a messaging platform that allows SMS messages to be programmatically scheduled and sent worldwide.[26] Questionnaire timing will be scheduled based on individual patient timelines, customised using the date of initial Gastric Alimetry™ test.

Statistical analysis

This protocol describes the development of a standardised and scalable data platform for tracking changes in symptoms, quality of life, and psychological outcomes over time. Exploratory and pilot analyses will be performed within acknowledged limitations of a non-randomised study design. Longitudinal assessments allow for the evaluation of the efficacy and utility of diagnostic assessments and treatments offered to patients. Monitoring within-subject changes has been shown to offer advantages in establishing causal relationships.[27] As data accrues over time, a large repository of longitudinal data will be available to compare the impacts of investigations, medication changes, and procedural interventions on patient-reported outcomes. Such causal inferences can lay the foundation for future randomised trials, informing power calculations, and identifying research priorities.

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Preliminary analyses will include descriptive comparative statistics, such as univariate between-group comparisons and also before-after testing (using individuals as their own control), where pre- and post-intervention paired statistics will be employed. Normally distributed data will be reported as mean (SD), and non-normally distributed data as median (IQR). Statistical comparisons will be performed using independent samples t-tests, analysis of variance (ANOVA), paired-samples t tests, or repeated measures ANOVA for normally distributed variables; Mann-Whitney U, Kruskal-Wallis tests, Wilcoxon signed-rank test, or Friedman's test for non-normally distributed continuous or ordinal variables; and $\chi 2$ tests or McNemar's test for categorical variables. Regression models will be used as appropriate for relevant outcomes including multivariate linear regression with adjustment for relevant demographic confounders. If sample sizes allow, mixed effects hierarchical models will be employed to account for natural clustering structures e.g., at the centre-level. Interclass correlations will be assessed via the interclass correlation coefficient. Model selection will be guided by parsimony, clinically plausible relationships between predictors and outcomes, and minimisation of the Akaike information criterion.[28] Missing data will be interrogated to assess if they are missing at random, and multiple imputation by chained equations or pairwise deletion will be employed as appropriate.

Study delivery and quality assurance

This longitudinal cohort study will be centrally managed by a steering group consisting of expert statisticians, data managers, and clinician scientists with oversight and guidance from key opinion leaders in the field of gastroenterology and gastrointestinal surgery. Regular data-auditing will be performed with communication between the steering group and individual sites. Training resources are available to ensure standardised use of the Gastric Alimetry™ system for all device users.[29]

Patient and public involvement

Several rounds of patient interviews were completed during the development stage of the Gastric Alimetry™ platform,[6,30] which informed the design and delivery of the app. Patient feedback will be actively sought at the time of each test and will contribute to ongoing development and data applications. Interviews with a range of patients, and gastric disorder patient advocacy group leaders have informed relevant study designs and key clinical questions; most relevant to this protocol being

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the impact on individual patient's continuum of care to reduce investigations, offer more actionable diagnoses, relationships to psychological health variables, and to direct more efficacious therapies.

Ethics and dissemination

Ethics approvals have been sought according to the requirements of each participating centre. At the lead site, the protocol has been approved in Aotearoa New Zealand by the Auckland Health Research Ethics Committee (AHREC; ref AH1130). Results will be submitted for conference presentations and peer-reviewed publication.

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Discussion

Gastric Alimetry™ is emerging as a significant new clinical test of gastric function combining gastric electrophysiology and concurrent symptom tracking.[1,6] This diagnostic tool offers a new paradigm for the investigation and management of patients with chronic gastroduodenal disorders,[2] but longitudinal data on outcomes is now required to define its impact on clinical workflows, diagnoses, and outcomes. Here we present a longitudinal cohort study protocol to assess the impact of Gastric Alimetry™ on patients' continuum of care; this will offer robust data for assessing relationships between clinical diagnoses, and management decisions on patients' symptoms, psychological symptomatology, and quality of life. These observational data will guide hypothesis testing, facilitating prioritisation and powering of future trials to advance the field.

This study also aims to generate evidence in support of putative mechanisms for poorly understood gastroduodenal symptoms in line with Tack et al's plausibility criteria for disease mechanisms in functional gastrointestinal disorders.[31] The longitudinal study design in particular is essential to generate evidence for the fifth putative criterion within this framework: 'Therapeutic response'/'Congruent natural history', which states that treatment aimed at correcting an underlying disorder improves symptoms, or, changes in symptom severity parallel changes in the severity of the disturbance.[31] This evaluations are also in-line with innovation frameworks which recommend large-scale longitudinal surveillance of outcomes when novel medical innovations such as the Gastric Alimetry™ system are employed in routine clinical use.[32,33]

We developed an integrated digital platform for robust data-linkage, accurate, and secure storage of longitudinal, repeated measures data. REDCap serves as the secure data storage infrastructure with the mobile MyCap app being the patient-facing platform for collecting patient-reported outcomes. Data completeness is encouraged through the use of Twilio, enabling automated, scheduled reminders. Scheduled tasks personalised to each individual patients' timelines facilitate scalability to a large volume of patients.[34] These data are then linked to gastric electrophysiological signal data after refined artefact rejection and algorithmic post-processing,[14] and the Gastric Alimetry™ App data which are stored on a HIPAA-compliant cloud platform.[35]

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Strengths and limitations

This study utilises validated, widely used instruments to measure self-reported gastrointestinal symptoms, quality of life, and psychological factors. Validated questionnaires were chosen for their external validity, brevity so as to be pragmatic with data collection, and reduced burden on patients. The use of self-administered questionnaires and diaries have also been shown to demonstrate increased reliability compared to interviews.[36] Despite these design elements, important limitations remain. We anticipate it will take time for sufficiently large cohorts to accrue prior to adequately powered inferential analyses can be performed. Also, despite efforts to rationalise questionnaire-volumes, it is important to capture the multifaceted contributors and sequelae of gastroduodenal symptoms on patients' lives. Given several different scales are being used, there is a risk of non-response.[34] To mitigate against incomplete data we employ timed reminders, use a patient-friendly app, and have rationalised the questionnaires to minimise questions being asked and maximise relevant outcome data collection. A 1-year follow-up was determined to be the most pragmatic for the majority of hypotheses aimed to be addressed using this protocol, however, in specific cases, longer follow-up than 1-year may be desirable, and as such the system described here remains flexible to such alterations. This protocol does not prespecify all elements of future analyses planned through this protocol.

In conclusion, we present a study protocol for a longitudinal cohort study of patients being investigated with body surface gastric mapping using the Gastric Alimetry™ system. These data will offer insight into the clinical utility and impact of Gastric Alimetry™, a new test to gastroenterology practice, and offer data to explore hypotheses in relation to impact on clinical decisions, treatment responses, and natural histories of disease.

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Figures

Figure 1: Overview of the Gastric Alimetry system and analysis pipeline. A) Gastric Alimetry system and App; B) Gastric Alimetry test procedure; C) Signal processing pipeline and end outputs.

Figure 2: Comprehensive overview of data being collected at baseline and each subsequent follow-up.

Figure 3: MyCap mobile application interface for daily symptom ratings. 0-10 Likert scale for stomach burn shown as an example.

Figure 4: Overview of data collection and follow-up

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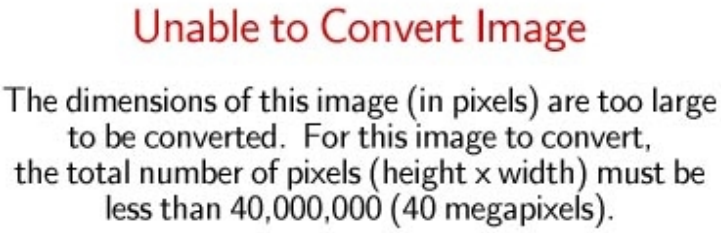

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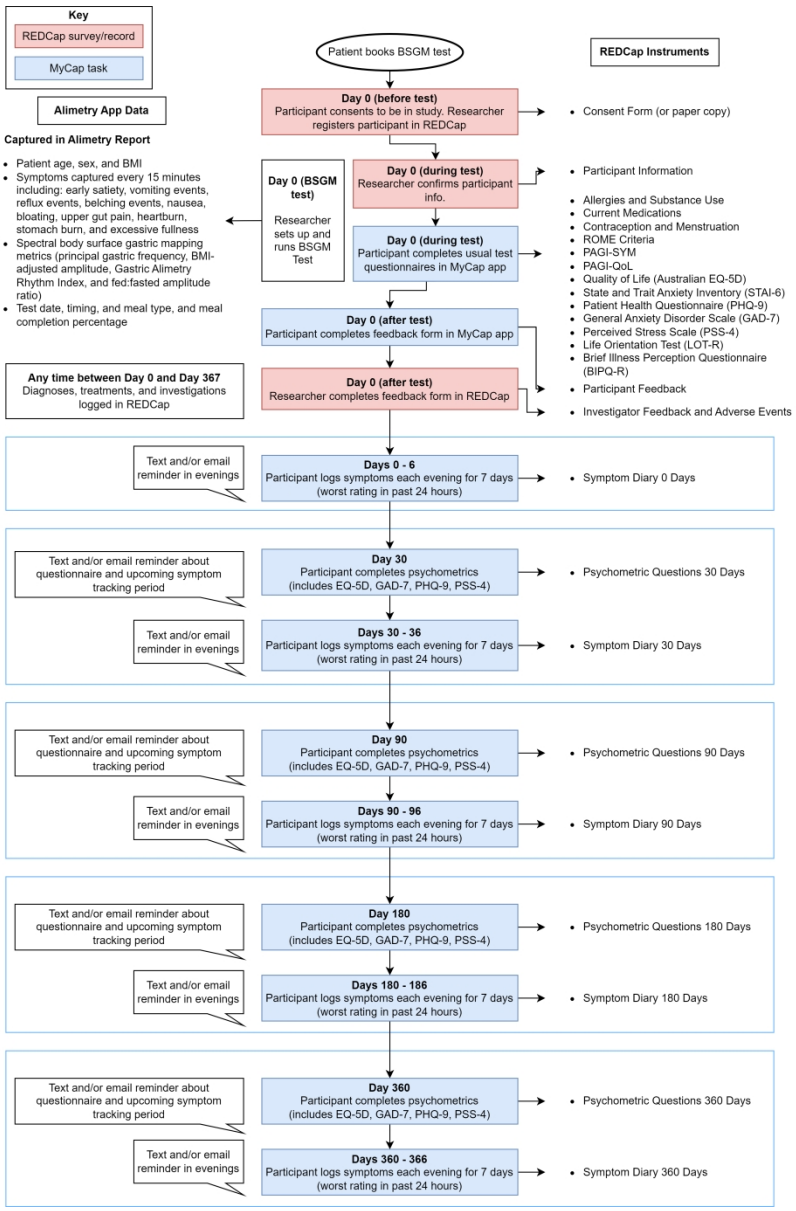

Figure 2: Comprehensive overview of data being collected at baseline and each subsequent follow-up.

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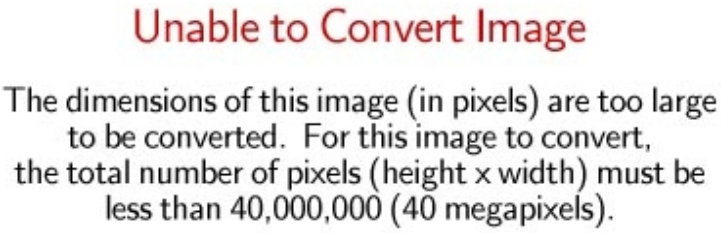

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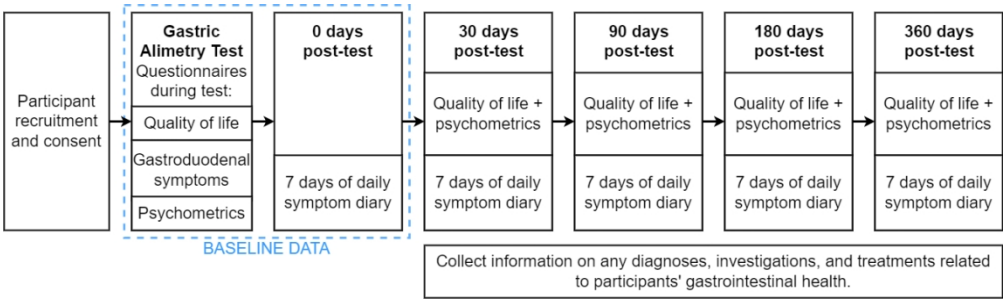

Figure 4: Overview of data collection and follow-up

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	1.0
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6-10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6-10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	6
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	6
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5-7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	NA
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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