Expanding the eligibility criteria for a no-biopsy diagnosis for coeliac disease in adults and children: An Individual participant data review and cost-effectiveness analysis

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Version control table

Version	Date	Changes and justification	Approvals
0.1	01/08/2024		NIHR approval Pending ethics approval
0.2	15/08/2024	Added detail on IPD review (WP1) following PRISMA-P guidelines	NIHR approval Pending ethics approval
0.3	23/09/2024	Added detail on lab survey (WP3)	NIHR approval Pending ethics approval
1	10/10/2024	Edits and additions to IPD data section. Trials registries included in information sources. Ethical approval	NIHR approval Approved by ethics
1	24/01/2025	Change to IPD storage arrangements for the duration of the project	DPIA approval

Background and rationale

What is already known

Coeliac disease (CD) is an autoimmune disorder, triggered by the protein gluten, found in wheat, rye and barley.(1) CD has an estimated global prevalence of 1%,(2) but because it can present with a wide range of non-specific symptoms, including anaemia, abdominal symptoms, and fatigue,(3) it is widely underdiagnosed.(4) The HLA-DQ2/8 risk genotype is required, although not sufficient, to develop CD.(5)

Traditionally, CD diagnosis followed a two-step pathway: a serological test for anti-gluten antibodies (e.g. Immunoglobulin A [IgA] against tissue transglutaminase [tTG], or endomysial [EMA]); followed by confirmatory endoscopy and biopsies.(6) Biopsy is generally safe but is invasive, expensive, potentially distressing and burdensome for patients, and has a small risk of complications. Most children require general anaesthesia. Although serological tests have a quick turnaround (usually 1-2 weeks), there are long wait times for endoscopies. In the UK, over 200,000 people are currently on the endoscopy waiting lists, and only 18% of services are meeting the routine endoscopy waiting time targets.(7)

In 2012, the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) published new diagnostic criteria that allowed some children to be diagnosed without biopsy. ESPGHAN considered the pathway “safe” if at least 95% of children who met the criteria had CD.(8) In 2018, Finnish guidelines recommended a no-biopsy pathway for adults (https://www.kaypahoito.fi/hoi08001), which was temporarily adopted by the British Society of Gastroenterology (BSG) at the start of the Covid-19 pandemic. In this interim guidance, adults aged <55 years, with >10x upper limit of normal for tTG antibodies, a positive EMA result, and no alarm symptoms (e.g. symptoms suggestive of gastro-oesophageal cancer) are eligible for a no-biopsy CD diagnosis.(9) Although currently in use, this no-biopsy pathway has not yet been adopted by national coeliac guidelines,(6) nor has it been implemented in all gastroenterology centres.(10)

To potentially allow more patients to benefit from a no-biopsy pathway, we need a better understanding of the optimal thresholds of serological tests (both for ruling in and out CD with a high level of certainty), to what extent thresholds could be lowered when combined with other tests (depending on test availability), and how these thresholds differ. Furthermore, we need to better understand the cost-effectiveness of these strategies in the whole population and in CD risk groups.

We recently completed a health technology assessment to determine the cost-effectiveness of active case finding strategies for CD in primary care (NIHR129020).(11) This included a systematic review of the accuracy of serological tests, a systematic review on CD risk factors, a prediction model to aid diagnosis of CD and a survey to explore the level of diagnostic certainty acceptable to patients, the results of which informed economic models.

Our previous work on CD case finding identified risk groups with increased risk of having CD (i.e. higher pre-test probability), of which the most important were type 1 diabetes, thyroid disease, and having a first degree relative with CD.(12, 13) The interpretation of our previous meta-analysis on serological test accuracy was limited by the substantial heterogeneity between the included studies. Accuracy statistics were reported across a wide variety of thresholds for test positivity across studies and reported in different units, with some studies not reporting the threshold used at all. Very few studies provided direct comparisons of the accuracy of serological tests, and those that did reported these comparisons at different thresholds. This meant that, despite the test accuracy review including 113 studies, accuracy estimates used for the economic model could only be based on single studies in adults and children, which resulted in uncertainty in the cost-effectiveness estimates of each case finding strategy. There was also a lack of information on how much tests are correlated

within patients with or without CD (as is likely in practice), which is important when estimating the accuracy of tests used in combination. If tests are highly correlated then there is little to gain from the second result, whereas if the correlation between tests is very low then a second test can substantially increase the overall test accuracy. Our review also identified variation in the definition used for the reference standard. Some used histopathology results with a Marsh score 2 and others Marsh score 3 to define CD. The importance of reliable estimates of the accuracy of serological tests was confirmed by our value of information analysis using the economic model. This analysis suggested that future research should focus on the accuracy of serological and HLA testing.

What this research will add

There is scope for expanding the eligibility criteria for no-biopsy pathways, which could be beneficial to patients and has the potential to be cost saving for the NHS.

The issues identified from our previous work can be addressed with an individual participant data (IPD) review. In an IPD meta-analysis, the original research data for each participant is sought directly from the researchers responsible for each study. Having access to the 'raw' data for each study enables data checking, thorough exploration, re-analysis of the data in a consistent way such that data can be meaningfully pooled, and will allow us to quantify the accuracy of each test at different thresholds and of tests used in combination. Although IPD meta-analyses are more time consuming and labour intensive than conventional systematic reviews, they can produce more reliable results and are considered the gold standard of systematic reviews.(14)

An additional source of uncertainty in our economic analysis was the costs of serological tests. These were informed through quotes provided by laboratories affiliated with our team, but we found costs to vary even within this small sample. Performing a UK wide survey would allow us to include more accurate estimates of testing costs and to identify the minimum costs at which these tests can be offered. A survey will also allow us to investigate the availability of serological tests, which will inform test combinations to investigate.

Why this research is needed now

Using conservative criteria, as are currently advised by the ESPGHAN no-biopsy pathway for children and the interim BSG guidance for adults, no-biopsy pathways have the potential to avoid 50% and 20-48% of biopsies previously recommended for the diagnosis of CD in children (8) and in adults (16), respectively. Our research aims to assess whether eligibility criteria for no-biopsy pathways for both children and adults can be expanded and better targeted, which may increase these numbers further. If more patients can be diagnosed reliably with (a combination of) serological tests, a substantial number of biopsies that are currently being conducted are unnecessary. This means that (1) unnecessary invasive tests can be avoided, (2) patients can be diagnosed quicker and can therefore start effective treatment earlier, (3) more patients can get the official diagnosis (as some patients currently choose not to have a biopsy and therefore don't get this), and (4) limited resources can be used more effectively.

Current guidelines for adults still recommend the use of a confirmatory biopsy in all patients, which is invasive, potentially distressing and burdensome for patients. Also, the majority of children are still diagnosed using biopsies.(17) Children require general anaesthesia to undergo a biopsy which is associated with risks of complications. Patients need to continue eating gluten for 6 weeks prior to biopsy, which can cause debilitating symptoms and worsening mucosal damage. Long waiting times for biopsy appointments can lead to uncertainty and delayed diagnosis for patients. For example, the PPI co-investigator who was recently diagnosed waited 3 months for the biopsy appointment and 6 weeks for the result. Delayed diagnosis predisposes to reduced well-being and incremental use of

medicines and health care services.(18) If CD is not diagnosed promptly and the condition remains untreated, difficulty absorbing nutrients may lead to malnutrition, anaemia and/or osteoporosis.(19) In the long-term, untreated CD increases the risk of serious complications, such as lymphoma, osteoporosis and small bowel cancer.(20, 21) Also for patients whose symptoms are caused by something other than CD the long waiting times mean continued uncertainty.

Unpublished findings from a free text analysis from a survey conducted as part of our previous work suggest that some people are not receiving an official diagnosis due to the current diagnostic pathway. These patients chose to start a gluten free diet based on their serology test results and found that their symptoms improved as a result. They were subsequently unwilling to reintroduce gluten into their diet, as is necessary for the biopsy to be accurate:

"Frightened to go back to eating gluten so I can be tested as I would be ill and confined to home for six weeks due to the effects of gluten on my system."

"I do wish I had a clinical diagnosis but going back to eating gluten makes me ill."

"My symptoms are so severe that I can't now do the gluten challenge to go through testing."

"They [GP] told me to go back to eating gluten and I refused (the diet reduced symptoms enough for me not to want to go back to suffering that badly again)."

No-biopsy diagnosis is not yet adopted by official guidelines for adults, so patients without an official diagnosis are missing out on care right now. The gluten free diet is expensive, which is an important barrier to adhering to the gluten free diet.(22) Gluten free products are available on prescription in some regions in the UK; however, CD patients can only make use of this if they have received an official diagnosis. In addition, diagnosed patients get signposted to support, invited for follow-up appointments, monitored for secondary conditions such as osteoporosis, and referred to a dietician to help with the transition to a gluten free lifestyle, so receiving an official diagnosis is important. Reducing the number of biopsies could also provide substantial healthcare savings, as it is estimated that up to 95% of CD diagnostic expenses could be spared by omitting the endoscopy and biopsy.(23) For example, one gastroenterology centre reported that a biopsy-based diagnosis costs £1300 compared to £65 for a serological-based diagnosis.(24) Unpublished data from Sheffield suggests that implementing the no-biopsy approach for adults on a national scale could save the NHS over £2.5 million in direct and indirect costs per annum by avoiding at least 3,000 endoscopies and preventing the loss of approximately 27,000 working hours. No-biopsy pathways may also free up capacity of gastroenterologists and reduce waiting times for biopsies, so they will become more accessible to patients who need them. Finally, earlier diagnosis and treatment for patients may lead to fewer follow-up appointments by reducing the risk of long term consequences of CD.

Aims and objectives

This research aims to determine the accuracy and cost-effectiveness of serological tests at different thresholds, singly and in combination, to optimise no-biopsy pathways for CD diagnosis in children and adults.

It will address the following objectives:

1. Estimate the accuracy of serological tests, individually and in combination, for CD at different thresholds (work package 1)
2. Develop potential clinical pathways (work package 2)
3. To evaluate the current landscape of CD diagnostic testing in laboratories across the UK, focusing on the availability and variability of serological tests (work package 3)

4. Estimate the cost-effectiveness of selected diagnostic strategies including different sets of eligibility criteria for no-biopsy pathways (work package 4)

Research plan

We will undertake four linked work packages to address each of our objectives:

Work package 1: IPD review

The IPD review will follow best practice recommendations from the textbook Individual Participant Data Meta-Analysis (2021).(25) We will form a consortium with the authors from eligible studies that consent to participate. The IPD review has been registered on PROSPERO (CRD42024582414) and we aim to publish the protocol as a journal article before data collection starts.

Eligibility criteria

The following inclusion criteria will be applied:

- Population: Children and adults with or without suspected CD
- Index tests: IgA/G tTG, IgA/G EMA, or IgA/G deaminated gliadin peptide (DGP).
- Reference standard: Duodenal biopsy
- Study design: Diagnostic cohort (one-gate) studies
- Publication data: within the last 20 years. This is a pragmatic choice, because based on initial efforts to contact authors, authors from studies older than 20 years did not respond or their IPD was no longer available.
- Data: 2x2 data must be reported or available upon request.

We will not apply language restrictions.

Search strategy and information sources

We recently completed a health technology assessment to determine the cost-effectiveness of active case finding strategies for CD in primary care (NIHR129020).(11) This included a systematic review of the accuracy of serological tests with searches conducted in 2020. We expect that all relevant studies published before 2020 have been identified by our previous review, which included 113 studies of which 69 are eligible for this IPD review.(26)

To identify relevant studies published since 2020, we will use a combination of two strategies. First, we will screen the list of included studies published since 2020 from a recent systematic review from our co-investigators that focused on studies reporting the sensitivity and specificity of IgA-tTG ≥10×ULN against duodenal biopsies (Marsh grade ≥2) in adults with suspected CD.(15) This review will have identified studies that are eligible for this IPD review between 2020 and 2023, but will not have included all eligible studies in this time period due to their focus on the 10×ULN threshold.

Secondly, we will run an update search to identity other relevant studies published since 2020. We will adapt our previously used search strategy,(26) which included more serological tests (that are no longer in use), to make it more specific to our IPD review. We will search MEDLINE, Embase, Cochrane Library, and Web of Science for relevant studies published since 2020. We will search trial registries; ClinicialTrials.gov as a minimum. We will supplement this search by screening reference lists of included studies and will ask the collaborative group to help identify eligible studies.

Data management

Identified references will be downloaded into EndNote 21 software for further assessment and handling. Rigorous records are maintained as part of the searching process.

Selection process

For studies identified via inclusion in either of the previous two reviews(26)(15), our previous data extraction tables will be used to check the eligibility of each study.

For the update search, study selection will be conducted in two stages using a dedicated systematic review software: (1) an initial screening of titles and abstracts against the inclusion criteria to identify potentially relevant papers and (2) screening of the full papers identified as possibly relevant in the initial screening. All papers excluded at the second stage will be documented along with the reasons for exclusion. Abstracts and full texts will be screened independently by at least two researchers. Disagreements about study eligibility will be resolved through discussion or by consulting a third reviewer.

Study level data collection process

Relevant data from eligible studies included in the previous reviews have already been extracted as part of those reviews. These data extraction tables will be checked by one reviewer for their completeness.

Data from new studies identified in the update search will be extracted using standardised data extraction forms a dedicated systematic review software. Data extraction forms will be piloted on a small sample of papers and adapted as necessary. In order to minimise bias and errors, data extraction will be performed by one reviewer and checked by a second. Disagreements will be resolved through discussion or referral to a third reviewer.

Data items

Key study characteristics will be extracted from each eligible study. These include study time period, location, design, sample size, clinical setting, inclusion and exclusion criteria, characteristics of the index test (e.g. commercial assay used for serological test), and reference standard (e.g. how many tissue samples were taken per biopsy). These details have already been extracted for all studies identified in our previous systematic review.

Risk of bias assessment

We will use the risk of bias assessment for the previous reviews, which will be checked by one reviewer for completeness. If previous reviews have used an older version of the QUADAS tool, we will update this to the newest version.

For all new studies, we will use the most recent version of the QUADAS tool to assess the risk of bias and applicability of each study (27, 28) and will adapt it for use in an IPD review following published guidance.(29) The quality of each study may help inform which studies are at high or low priority for IPD retrieval and will allow us to do a sensitivity analysis on high quality studies. Where the risk is ‘unclear’ due to missing information we will contact the authors and request this information as part of the IPD collection process.

IPD collection process

We will invite authors of eligible studies to collaborate and provide anonymised IPD. We will set up a collaborative group (the *No-Biopsy Consortium*), draft a consortium agreement, set up data sharing contracts, and offer the opportunity for collaborators to share authorship.

Where possible, we will use personal relationships to approach authors. If we don’t have personal relationships to the authors, we will contact the corresponding author, any of the co-authors, and/or

the institution that sponsored the research directly. We will check the terms of funding of selected studies if this included a requirement for data to be shared.

Our initial approach is to first contact authors of the subset of studies that report on the accuracy of at least two serological tests. These studies are considered a priority as these allow us to investigate the accuracy of combinations of tests. We will contact authors from the remaining studies in order of priority, starting with the most recent publications (studies older than 15 years were more likely to have deleted the data and less likely to respond), larger studies (>200 participants), studies that we have assessed to be at low risk of bias, and studies reporting relevant patient characteristics.

IPD data items

Where authors agree to contribute to our IPD meta-analysis, we will request the following participant-level variables:

- Quantitative serological test results for tTG, EMA, or DGP (IgA/G levels). These will be used as the index tests in our analyses to calculate diagnostic accuracy measures, such as sensitivity and specificity. The quantitative values are essential to calculate diagnostic accuracy across all thresholds. If more than one test is performed, data on whether the tests are done on the same or separate samples.
- Histopathology results (Marsh score), which will allow us to apply the same Marsh score threshold for all patients in defining the reference standard to evaluate the serological tests against.
- Time between the serological tests and biopsy.
- Total IgA levels. Selective IgA deficiency is almost 10 times more common in patients with CD compared with the general population and total IgA levels affect the reliability of the tTG IgA and DGP IgA tests and may be considered as part of a diagnostic pathway.
- Patient demographics (age, sex, and ethnicity), if available, will allow us to explore whether the accuracy of serological tests or their combination varies by these characteristics. We will be able to consider if certain pathways or thresholds are feasible for certain subgroups.
- Patient symptoms, which may allow us to stratify the analysis by asymptomatic and symptomatic patients. Our previous work with patients has shown that people without symptoms have a lower tolerance to diagnostic uncertainty, whereas people with symptoms have a higher tolerance for diagnostic uncertainty. Symptomatic will be defined as having one or more of the following symptoms: gastrointestinal symptoms, faltering growth, fatigue, weight loss, mouth ulcers, iron, vitamin B12 or folate deficiency. If possible, we will collect information on whether the cause of iron, vitamin B12 or folate deficiency is known or unknown.
- Risk factors, which may allow us to stratify the analysis by risk groups that were identified in our previous work (diagnostic indicator review and prediction model): family risk (family history, or first-degree relative, or second degree relative with CD), type 1 diabetes, migraine, anaemia, osteoporosis, chronic liver disease, thyroid disease, irritable bowel syndrome, subfertility or pregnancy loss, and HLA DQ risk genotypes. For instance, serological thresholds may be lowered further for patients who have certain risk factors for CD given higher pre-test and positive predictive values in these patients.
- Any information on gluten free diet at time of testing (both biopsy and serology). E.g., whether patients were following a gluten free diet, whether they have been eating gluten for 2/3/4 weeks before testing.
- Test kits used. There are many different assays from different suppliers currently in use; if there is sufficient data available, we may be able to account for this in the analysis.

In addition, we will request study level data that are missing from the papers; in particular, details on how biopsies were performed (which will allow us to judge the reliability of the biopsy results),

details on the serological assay(s) used, and any other missing information needed to update the initial QUADAS assessments.

IPD management and storage

We will receive anonymised patient level datasets from collaborators, containing one row per patient. Data checking and cleaning will be performed as and when datasets are received, so that we can ask for clarifications or additional information from the study authors as soon as possible. We will create a new cleaned dataset by combining all these datasets. This new dataset is of long-term value and should be shared and preserved, so that other researchers can add new data or address other research questions.

We will set up data sharing agreements (as part of a consortium agreement) with the study authors' institutions aiming to minimise restrictions on reuse. We will request permission to publish on data.bris and permission to share the data with other researchers in the future using Bristol's established data access release process.

For the duration of the project, data will be stored a secure working environment for data processing and handling at the University of Bristol, such as the Bristol Medical School (BRMS) central filestore or a project SharePoint folder. In all cases access will be restricted to named team members within the University of Bristol.

Data will be kept for up to 20 years, subject to data sharing agreements. Once the project is finished, the created IPD dataset will be stored by The University of Bristol Research Data Storage Facility (RDSF), which provides secure, long-term storage for research data. This major investment provides nightly backup of all data, with further resilience provided by three geographically distinct storage locations. A tape library is used for backup purposes and also for long-term, offline data storage. Only authorised users can access data stored within the RDSF. The RDSF is managed by Bristol's Advanced Computing Research Centre (ACRC) which has a dedicated steering group and a rigorous data storage policy. The RDSF upholds and reinforces Bristol's wider Information Security policy.

Data will be published through the University of Bristol Research Data Repository (data.bris) who offers controlled access of the data. We will share data once the funders main report (NIHR HTA) has been accepted for publication. IPD will be made available to approved bona fide researchers only, after their host institution has signed a Research data access agreement for restricted data.

Summary of statistical approaches

We will verify that we can reproduce the sensitivity and specificity estimates from the original manuscripts. If the estimates differ substantially from the original manuscripts, we will liaise with the study authors to investigate the causes of this.

We will standardise all serological test results by converting them to x times the upper limits of normal (ULN).

We will produce pooled results of the accuracy of each test at each threshold by applying a separate bivariate meta-analysis model,(30, 31) which is the recommended approach.(25) We will explore the feasibility of doing a one-stage IPD meta-analysis, where IPD from all studies are analysed in a single step using an appropriate model that accounts for clustering of participants within studies. If this is not feasible, we will use a two-stage IPD meta-analysis approach, where the IPD are first analysed separately within each study to obtain aggregate data after which these aggregate data are combined in a standard meta-analysis model.(32)

We will additionally categorise each participant in each study as positive/negative on each of the testing strategies developed in work package 2. After doing so, we will perform meta-analysis to estimate the accuracy of these strategies using the same methods described above.

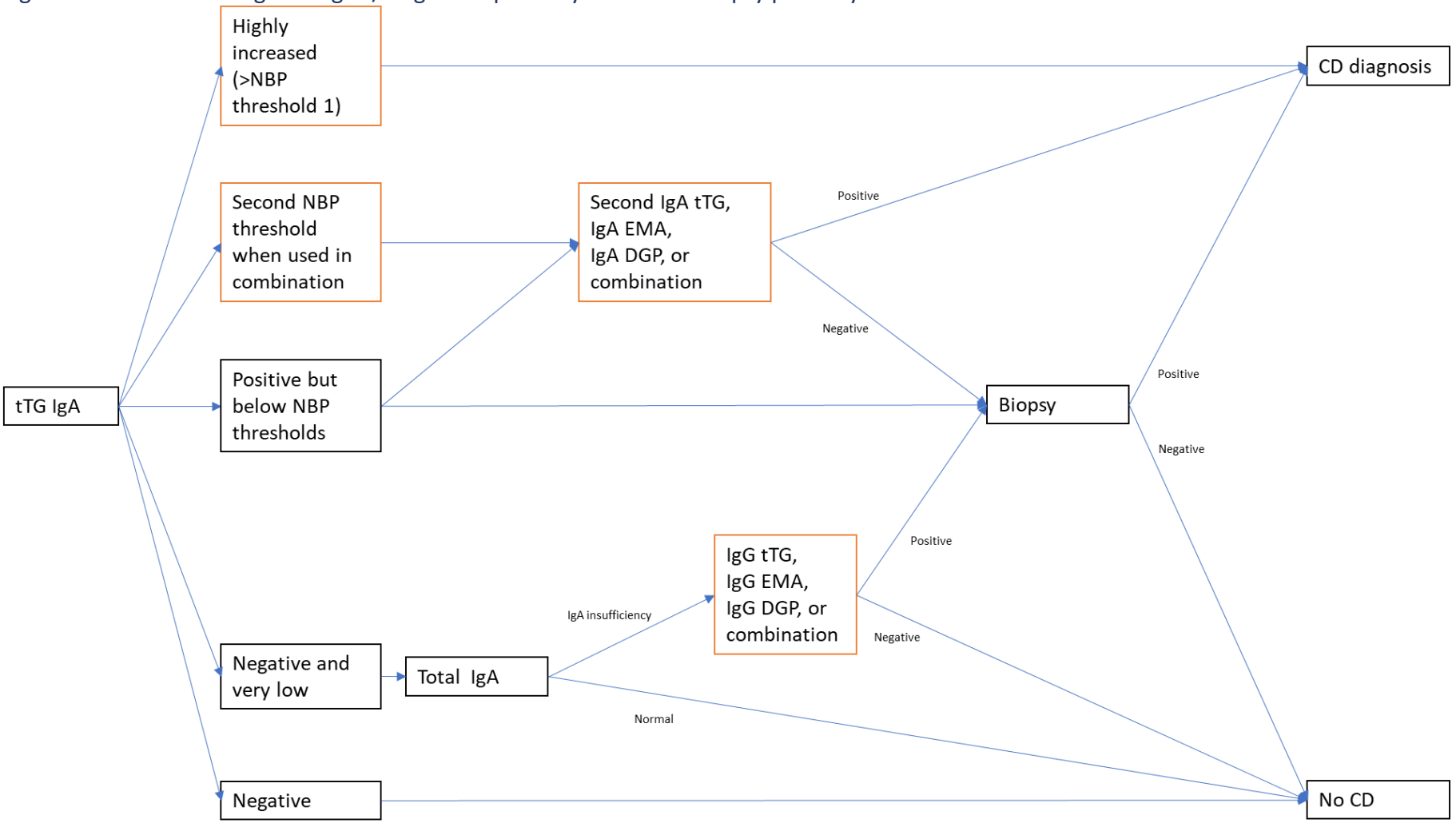
We will use pooled estimates of sensitivity and specificity to produce estimates of positive and negative predictive value (PPV and NPV) at prevalence of average primary care and secondary care populations. We will determine at which thresholds PPV and NPV are sufficiently high for tests to be used in isolation or in combination (using testing strategies developed in work package 2) to rule in or rule out CD.

If we have sufficient data, we will explore heterogeneity by age group, sex, whether patients were symptomatic or asymptomatic, or having any of the following risk factors: family risk (family history, or first-degree relative, or second degree relative with CD), type 1 diabetes, migraine, anaemia, osteoporosis, chronic liver disease, thyroid disease, irritable bowel syndrome, subfertility or pregnancy loss, and HLA DQ risk genotypes. We will follow published guidance on handling missing covariate data using multiple imputation.(25)

To investigate the possibility of bias due to selective availability of IPD, we will compare the IPD meta-analysis accuracy estimates with estimates from aggregate data meta-analysis on all studies that were eligible for inclusion in the IPD review. This will allow us to judge whether the sample of studies included in the IPD meta-analysis is biased.

If possible, we will perform a sensitivity analysis in which we restrict analysis to only studies assessed as overall low risk of bias and studies that followed best practice regarding the biopsy (leading to more accurate results).

Figure 1. Potential testing strategies/diagnostic pathways. NBP: No-biopsy pathway



Work package 2: Clinical pathways/testing strategies

We will develop potential no-biopsy pathways for children and adults. Pathways could include single tests, a combination of tests, or tests combined with other factors, such as risk factors or other clinical information. The information that we will be able to consider depends on the availability of IPD and covariates. See Figure 1 for examples of testing strategies.

We will conduct a Delphi procedure to refine these testing strategies to ensure they are acceptable and realistic/practical, based on current clinical practice. The Delphi method is one of the most widely-used and most rigorous consensus methodologies and has been used extensively in healthcare, in particular for developing guidelines.(33) The Delphi method it is an iterative process with several rounds of questions to panel members and each round summarised feedback from the previous round is shared anonymously. The benefits of using Delphi methodology are that it allows for a wide range of knowledge and experience to be involved and that it prevents group members from conforming with the opinions of others.

We will recruit panel members from within the UK because we want to develop pathways that can be implemented in the UK (however, they should be easily adaptable to other countries and healthcare systems). We are planning to recruit a diverse group of panel members from different areas within the UK, such as gastroenterologists who work with children and ones who work with adults, clinicians with different levels of experience, patients representatives who were diagnosed recently with and those who were diagnosed without biopsy, including parents of children with CD, and other relevant stakeholders, such as policy makers, clinical guideline and reference groups, and NHS commissioners.

We are aiming to recruit 4-6 paediatric gastroenterologists, 4-6 adult gastroenterologists, 8-12 GPs, 4-6 adults with CD, 4-6 parents of children with CD, and 8-12 other relevant stakeholders as defined above. The final Delphi panel will have 32-48 members.

We will recruit gastroenterologists via specific gastroenterologist platforms that our co-applicants have access to. We will recruit patients amongst Coeliac UK members using their channels and we will recruit GPs with help of the NIHR Clinical Research Network (CRN). We will recruit additional stakeholders by contacting members from current or previous clinical guidelines groups, such as BSG/NICE and ESPGHAN, commissioners through our contacts with Integrated Care Boards, and policy makers through NICE, the professional gastroenterological or coeliac society professional groups.

The Delphi panel will help define how the pathways will work between primary and secondary care. One of the main concerns with the no-biopsy approach is that many patients with positive serology at any level will be incorrectly labelled as having CD in primary care or started on a "trial" of gluten-free diet. Before the pandemic, nearly 1-in-3 patients with positive serology in primary care were not referred for endoscopy and biopsy.(34, 35) Therefore, having clear diagnostic pathways, refined by primary and secondary care clinicians, would safeguard the diagnosis and provide a framework for optimal adherence to guidelines.

The Delphi panel will also help identify thresholds that are likely to be useful clinically, including (i) a rule-in threshold, at which we would be confident of CD without a biopsy, (ii) a rule-out threshold, at which we could confidently exclude CD without biopsy, (iii) best trade off threshold balancing the net benefit of identification of true positives and false.(36)

Work package 3: Survey UK labs on test availability and costs

Aim

To evaluate the current landscape of CD diagnostic testing in laboratories across the UK, focusing on the availability and variability of serological tests.

Objectives

- To collect information on the availability of CD diagnostic tests across UK laboratories.
- To evaluate the variations in testing kits and the different thresholds used among different laboratories
- To assess the costs associated with CD diagnostic tests.
- To examine the turnaround times for reporting results from CD diagnostic tests.
- To evaluate the reporting of test results by laboratories, including the communication of test interpretation and follow-up recommendations.

Methods

Study design

This is a nationwide cross-sectional, observational study using a telephone survey of biomedical scientists and laboratory managers based in NHS hospital trusts providing coeliac serology testing services in England, Wales, Scotland, and Northern Ireland.

Questionnaire development

We will develop the survey questionnaire in collaboration with the clinicians and health economists on the project team. We will discuss the survey questions with the PPI panel to make sure we are not missing any important information for patients. Finally, we will involve a couple of labs that we will recruit through contacts in our research team. These labs will be able to pilot the survey, to check the questions are not ambiguous or commercially sensitive and advise us on dissemination to improve response rates. If certain questions are commercially sensitive we may make these questions optional to still be able to collect other key outcomes.

Eligibility criteria

Inclusion criteria

- Laboratories of NHS hospital trusts that offer coeliac serology testing across the UK.

Exclusion criteria

- Laboratories that do not perform coeliac serology testing.
- Private laboratories.
- Laboratories outside the UK.

Sample identification, recruitment and consent

The target population includes biomedical scientists and laboratory managers working in NHS hospital trusts that offer CD serology testing.

Sources for identification

We will obtain a list of all NHS hospital trusts in England, Wales, Scotland, and Northern Ireland via the NHS digital database.

Recruitment and consent process

We will conduct a preliminary search to compile contact information (phone numbers or email addresses) for biomedical scientists and laboratory managers in each identified NHS trust. The aim would include at least one key contact from each NHS trust identified.

A member of the research team will contact participants via telephone to explain the study and request their participation. During the telephone call, verbal consent to participate in the study will be obtained. We will ensure participants understand their right to withdraw at any time without any repercussions. We will schedule follow-up calls for those who express interest but do not complete the survey during the initial call.

Cost estimates

Cost estimates for CD diagnostic tests will be gathered from NHS reimbursement schedules and company pricing.

Data collection and analysis

Survey administration

A structured questionnaire will be developed to capture the following key variables:

- Laboratory location (NHS trust, region).
- Availability of serological tests (tTG and EMA).
- The type of assay used for tTG testing and how results are reported (qualitative or quantitative).
- The upper limit of normal of tTG titre reported by individual laboratories.
- The automatic reporting of total IgA concentration when CD serology is requested.
- Turnaround times for reporting results.
- The communication of test interpretation and follow-up recommendations.

Data input

All collected data will be inputted into a standardised Excel spreadsheet to facilitate organisation, analysis and reporting. The spreadsheet will include pre-defined columns for key variables such as laboratory name, contact details, availability of tests, turnaround times, and any additional notes.

Data analysis

- Data will be cleaned and organised within the standardised Excel spreadsheet to ensure it is ready for analysis.
- Descriptive statistics will be used to summarise the key variables, including frequency distributions and percentages.
- All analyses will be performed using Stata version 18 (StataCorp, College Station, Texas, USA).

Data management

All participant responses will be anonymised, and data will be stored securely following The General Data Protection Regulation guidelines. Data collected will be stored on a secure server, and access will only be granted to the research team.

Work package 4: Cost-effectiveness analysis

We will follow best practice guidelines of the UK National Institute for Health and Care Excellence (NICE), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), and the Society for Medical Decision Making (SMDM).(37) The unit of effectiveness will be the Quality Adjusted Life Year (QALY). Health utilities will be associated with each of the states in a multistate model which, when combined with health state occupancy over time, allows total QALYs to be

estimated. The NICE reference case will be followed, where appropriate, which includes using a 3.5% discounting rate for costs and QALYs, and an NHS and personal social services (PSS) perspective.(38) Results will be presented as net monetary benefit (NMB).

The feasibility of a societal perspective will be considered as many of the costs of a gluten free diet (GFD) are not covered by the NHS.(39) This has significance for the costing of false positives, as the primary impact is to switch to GFD, before the falsely diagnosed patient finds it has limited benefit.

The impact of uncertainty around the cost and utility impact of GFD, and adherence to GFD given a diagnosis of coeliac disease, will be assessed through probabilistic analysis.(40, 41) All uncertain parameters will be associated with a probabilistic distribution and propagated through the model. Results will be presented as a an NMB with 95% credible intervals and cost-effectiveness acceptability curves (CEACs). Deterministic analyses, where each parameter is fixed, will not be conducted.(40, 42) Value of information analysis will be used to test the sensitivity of our decision to individual and groups of parameters.(43, 44)

Reducing the lifetime costs accrued by coeliac patients will allow greater resources to be allocated to other areas of the health service, such as colorectal cancer screening. Cost-effective decision making for coeliac screening therefore helps achieve the overall aim of allocative efficiency in the NHS.

We will build on our existing economic model, developed as part of our original grant (NIHR129020),(11) with the diagnostic test accuracy estimates per threshold from the IPD analysis (work package 1) and the costs of the serological tests from the survey (work package 3). Our previously developed model used a decision tree to represent diagnostic pathways and a Markov model for long-term disease progression and complications. The decision tree will need to be adapted to represent no-biopsy pathways from work package 2. We will estimate the cost-effectiveness of each of these pathways, as well as how many biopsies can be avoided, how many CD patients may be missed or put on a gluten free diet unnecessarily, and what the time will be between CD suspicion and diagnosis. Cost-effectiveness will be compared to that of current no-biopsy pathways, which are the ESPGHAN no-biopsy pathway for children and the BSG interim no-biopsy pathway for adults. They will also be compared to a scenario where every patient undergoes a confirmatory biopsy, as was the case for adults before the start of the pandemic.

We will build on the exploration of heterogeneity in test accuracy of work package 1 by modelling cost-effectiveness in identified subgroups. Such subgroups include different age groups, sex, symptomatic versus asymptomatic patients, patients with a first degree relative or an HLA risk genotype, or type 1 diabetes. The risk of complications that were included in the Markov model, such as osteoporosis, non-Hodgkin's lymphoma, and anaemia, may depend on the subgroup being modelled. This variation may lead to different pathways being most cost-effective in different subgroups. We will use targeted literature reviews to estimate subgroup specific risks for the subgroup-specific Markov model(s). Subgroup specific and whole-population average cost-effectiveness analyses will be conducted.

We will consider whether it is necessary to adapt our approach from cohort level models for each subgroup to an individual level model which correctly represents population heterogeneity. Individual level models also allow waiting times for biopsy to be explicitly modelled, which would capture a key advantage of no-biopsy strategies.(45) State-based or event-event individual level models allow granular modelling of interactions between patient risks and rates of complications.(46) Depending on PPI feedback, results of the IPD meta-analysis, and clinical advice, complications may be added to our existing model, with rates informed by analyses of routinely

collected healthcare data, using existing data from Clinical Practice Research Datalink (CPRD) linked with Hospital Episode Statistics (HES) from our previous HTA grant.

Ethics

The IPD review has received a favourable opinion from the Faculty of Health Sciences Research Ethics Committee (FREC) (Ref: 21979). We used the NHS Health Research Authority (HRA) decision tool to determine the need for ethics approval for the lab survey (WP3). As the survey is considered a service evaluation, ethical approval is not required. However, we will follow best practices for ethical conduct.

We already have ethics to a CPRD dataset including coeliac patients and matched controls, which was used to develop the economic model of our previous HTA project (NIHR129020). WP4 aims to update the economic model based on results from work package 1, work package 2, and work package 3 with better estimates which falls within the scope of the original ethics application.

Patient and public involvement

Our team includes two patient representatives, one who has recently been diagnosed with CD after blood tests and biopsy, and the second who has a son, husband and father with CD. The team also includes Heidi Urwin from Coeliac UK who will link us to the wider coeliac community. The study investigators also bring a patient perspective as one team member as a son with CD and another has a sister with CD. PPI applicants have informed the study design and will be invited to join regular team meetings to provide patient perspectives on the proposed research to ensure that it addresses patient needs. We will recruit further patient representatives to form a PPI panel who will be involved in all four components of this project. For instance, we will discuss possible alternatives to a CD diagnosis based on a biopsy to find out which are realistic and acceptable to patients and we will discuss the survey with a PPIE panel to ensure that the survey does not miss any important information for patients.

Dissemination and stakeholder engagement

Results will be disseminated widely to clinicians, policy makers, and patients. Our dissemination and impact strategy will be informed by the theories and practices of Knowledge Mobilisation (KM). We will work in close collaboration with the implementation team at ARC West and will be supported by the specialist support of a Communications Officer.

We anticipate a minimum of three peer reviewed articles and two presentations at national and international conferences. We will work with our PPI team to produce a plain language summary and visual infographics, using guidance that we developed for NICE.(47) Coeliac UK will help us to disseminate these to patients. Coeliac UK is the UK charity that has been supporting people with CD and other gluten related conditions for over 50 years. It has an active membership of over 60,000 and since its inception it has had a membership equivalent to the diagnosed CD population within the UK. It has a strong social media presence with around 100k followers on Facebook and further followers on Twitter (now X) and Instagram, so is well placed to engage digitally with the wider community in addition to its printed publications for members.

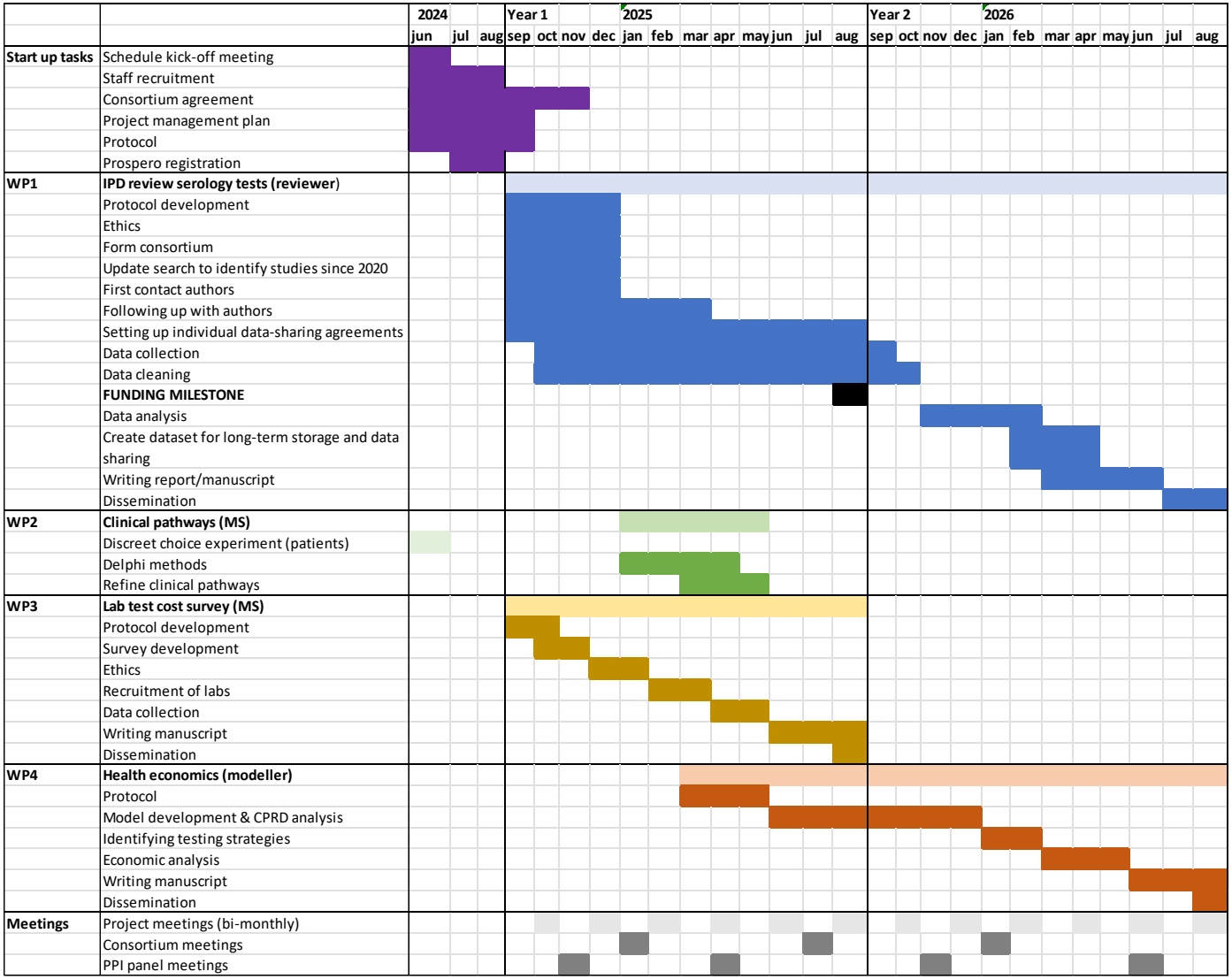
We will make the anonymised IPD dataset available to other researchers (subject to data sharing agreements with the study authors and participants' consent in the original studies), who can request access and use it for future research, in line with NIHR Open Research Data Policy. Data will be published by the Research Data Storage Facility of the University of Bristol.

To maximise the benefit of our research we will aim to disseminate our findings to guidelines committees and the coeliac committee as soon as possible. Our aim is to raise awareness of the no-biopsy pathways among coeliac patients and change practice through changing guidance. Our close collaboration with Coeliac UK and having guidelines committee members on our research team will enable us to do this effectively. We will reach out to guidelines committees early in the project to make them aware of our work. We will produce targeted outputs, including plain language summaries for patients that we distribute via Coeliac UK, short reports for policy makers, conference abstracts and manuscripts for researchers and clinicians. In Sheffield, we organise several meetings throughout the year, which are attended by Gastroenterologists from all over the UK where we will showcase the outputs of this research.

Expected research outputs

- IPD Protocol, which will be published in a peer reviewed journal if possible and otherwise will be published online on an open access website, such as OSF.oi.
- IPD review and meta-analysis. This paper will describe the findings of the IPD review (results work package 1). It will show the diagnostic accuracy of different no-biopsy diagnostic pathways, such as different combinations of tests, single tests used at different thresholds, or different thresholds used for certain patient subgroups/risk groups.
- A paper describing the results of the Delphi procedure, which will be several acceptable and realistic no-biopsy pathways (work package 2).
- Survey of serological tests used in the UK. This paper will describe the range of assays used, at which threshold, and the variation in costs (work package 3).
- Health economics paper. This paper will describe the model of cost effectiveness of different diagnostic pathways (work package 4).
- NIHR HTA report
- Conference presentations. We aim to present the results of the programme at the Coeliac UK conference, at a gastroenterology conferences, such as BSG Live, UEG Week, DDW, and The International Society for the Study of Celiac Disease conference which will be in Sheffield next year (no funding is requested for the latter as our team members are organising this conference and are based in Sheffield).
- We will create tweets and plain language summaries of the results for patients and carers.
- Database for CD research

Project timetable



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