Boston Children's Hospital

CHeRP IRB Additional Protocol Information:

In addition to the CHeRP SmartForms, all protocols must include the following sections. If a section is not applicable for the current protocol please indicate why this is the case. Please note that a complete protocol consists of the CHeRP forms and the information provided in this form.*

TITLE: Do GIPs Improve Practice (GIP) at Home? Effects of home gluten immunogenic peptide testing on children with celiac disease

A. Specific Aims/Objectives

1. **Determine the prevalence of biomarkers of gluten ingestion in urine of American children with biopsy-confirmed celiac disease who are trying to follow a gluten-free diet.**
2. **Determine whether knowledge of detection of biomarkers of gluten exposure affects:**
   (a) the prevalence of detection of biomarkers of gluten exposure in urine and/or stool;
   (b) subsequent gluten-free diet adherence by children with celiac disease;
   (c) celiac disease symptoms;
   (d) health related and disease specific quality of life; or
   (e) absences from school and extracurricular activities.

Hypotheses

- Gluten exposure is common among children with celiac disease who are trying to follow a gluten-free diet
- Frequency of gluten exposure is modifiable and awareness of GIP detection leads to
  - improved subsequent adherence;
  - reduced symptoms;
  - improved quality of life; and
  - decreased absence from school and extracurricular activities.

B. Background and Significance

Celiac disease is a systemic immunological disorder which affects 1% of Americans and often develops in childhood[1]. The hallmark of celiac disease is immune mediated damage to the villous lining of the small intestine that is perpetuated by gluten[1]. Manifestations of celiac disease may be non-specific, such as abdominal pain, irritability or poor growth. Untreated or partially treated celiac disease is associated with persistent symptoms and complications including short stature, nutrient deficiencies and lymphoma. Successful treatment of celiac disease requires a strict gluten-free diet. This involves elimination of wheat, rye, barley and most oats, which is challenging to implement for both practical and social reasons[2–4]. Consequently, patients with celiac disease often report decreased health-related quality of life and a high treatment burden compared to those with other chronic diseases, including type 1 diabetes and inflammatory bowel disease which are often perceived as more severe than celiac disease[5]. Gluten is ubiquitous and tasteless, so unintended gluten exposures are inherently difficult to detect and are likely to be more common than is appreciated. In a survey of highly adherent children, more than 50% reported symptoms attributed to gluten exposure[6]. Among the patients who are followed at Boston Children's Hospital, 60% have persistent symptoms at 6 months, of which over 30% are attributed to gluten exposure[7].

Challenges of following a gluten-free diet

Patients with celiac disease are well aware that the consequences of consuming gluten are serious and many report that fear of cancer and death is a motivation for persevering despite the challenges and restrictions of a GFD[8]. Tremendous motivation is required because adopting a GFD is a significant undertaking. The ability to maintain a GFD depends upon many environmental and individual factors and is highly variable. Self-reported rates of strict adherence among adults with celiac disease range from 36-96%[9]. Reported rates of mucosal recovery at 24 months are lower and range from 36[10]-60%[11].

Food labelling may be inaccurate[12] or difficult to interpret[13–15] and complete ingredient lists are not always available, particularly when eating food prepared by others. Additionally, cross-contact between gluten-free and gluten-containing foods may occur at any point from planting through processing and serving. Thus, ingestion of small amounts of gluten may be relatively common. Small amounts of gluten may not produce symptoms, so there is not always a 'feedback loop' to alert to accidental gluten exposure; nevertheless, these silent gluten exposures may interfere with mucosal recovery[16].

These intricacies are not appreciated by all patients with celiac disease. Even those who report strict avoidance of gluten often discover they are consuming gluten during diet review with a dietitian[17,18]. Among members of the Canadian Celiac Association (CCA), 85% could not determine whether foods were gluten-free some or most of the time[13]. In our own studies of patients with celiac disease, we have found that persons with celiac disease have difficulty identifying whether foods may contain gluten and that the ability to identify potential gluten-containing foods is poor even among those who report strict adherence to a GFD[19].

Challenges in monitoring patients on a gluten-free diet

This proposal addresses a major gap in celiac disease research and patient care: the lack of a validated measure to assess gluten-free diet adherence. Clinicians and clinical researchers alike currently rely upon self-reported adherence, dietitian assessment, serology and duodenal biopsy, each of which has significant limitations for repeated use in regular follow-up over time. Duodenal biopsy is the gold standard for demonstrating mucosal recovery[20], but it is invasive, uncomfortable and costly. Diet review by an expert dietitian is neither standardized nor widely available and is insensitive to silent gluten ingestion. Serologic tests for tissue transglutaminase (TTG) and endomysial (EMA) antibodies are very accurate for diagnosis, but are not responsive to intermittent gluten exposure in patients on a gluten-free diet[21]. Consequently, the patient must implement the diet without the tools necessary to assess whether self-management has led to the sustained mucosal recovery required to prevent cancers and ensure optimal long-term outcomes.

The ideal test for lifelong monitoring of patients with celiac disease must have three properties. First, it must be sensitive to gluten ingestion because this feedback is useful to direct the patient to adjust self-management strategies. Second, the tool must be predictive of mucosal recovery because this is the clinically important outcome in celiac disease[10]. Equally necessary, given that celiac disease is a lifelong condition and following a GFD is an ongoing process and not an endpoint, it must be practical to repeat the test frequently across the lifespan. None of the currently available tools satisfy these requirements[22].

C. Preliminary Studies

Although adherence to a gluten-free diet is the primary treatment for celiac disease, there are few studies which have measured either gluten intake or excretion to assess gluten-free diet adherence[23–25]. Most prior studies rely upon proxy measures of adherence such as self-reported adherence, dietitian assessment, serology or mucosal recovery. In this study, we will investigate the clinical role and impact of measurement of gluten immunogenic peptides in urine and feces during routine follow-up of children with celiac disease.

As discussed above, gluten is a plant storage protein found in the prolamine fraction of wheat (gliadin), barley (hordein), and rye (secalin). The antigenic portions of these proteins are proline rich and inherently resistant to endogenous human proteases present in the gastrointestinal tract[26]. This

facilitates exposure of the small intestinal mucosa to antigenic gluten peptides and enables passage of these intact fragments through the GI tract[24,25]. These properties will be exploited in this study to examine the reliability of stool assays for gluten ingestion.

The CODEX Alimentarius standards not only define thresholds for the gluten content of gluten-free products, but also the methods for determining the gluten content[27]. Currently, the standard is based upon the R5 antibody which recognizes the sequence QQPFP (glutamine-glutamine-proline-phenylalanine-proline)[28]. Several ELISA based assays are commercially available. These are most commonly employed by companies which manufacture gluten-free foods to determine the gluten content of the raw ingredients and/or the final product. There are limited studies reporting their use to determine the gluten content of various flours and packaged foods. These tests are not widely available for patient use. Compared to other methods for measuring proteins present at low concentrations (e.g., mass spectrometry[29], aptamers[30]), immunoassays produce results more rapidly, with less sample processing, and at a lower cost[31].

Other antibodies have also been described, including G12, which recognizes the principal antigenic sequence in gliadin (PQPQLPYP)[32]. The G12 antibody has been used to determine the gluten content of beer as well as to detect gluten in the stool[24] and urine[23]. Initially, a graded gluten challenge protocol was used to determine the relationship between the amount of gluten ingested and the amount of gluten immunogenic peptides (GIPs) detected in fecal extracts using an ELISA technique. Using the G12 monoclonal antibody, GIPs could be detected in stool after ingestion of as little as 50 mg of gluten (equivalent to a penne noodle)[24]. This amount is clinically relevant as estimated ingestion of as little as 10-50 mg of gluten per day has been associated with mucosal damage in patients[33,34]. The time from ingestion to excretion of gluten peptides in stool was observed to be between 2 and 4 days.

In subsequent study of 188 patients with celiac disease on a GFD, 73 positive controls on a gluten-containing diet and 11 negative controls (formula fed infants who had not been exposed to gluten), the sensitivity and specificity of GIP testing in stool were 98.5% and 100%, respectively[25]. Among patients with celiac disease on a gluten-free diet, 30% had detectable levels of GIP in their stool, of whom 70% appeared to be adherent based upon self-report questionnaire and four day food record. It is unknown how these tests perform in a clinical setting.

Further studies have demonstrated that GIPs are also excreted in urine within 24 to 48 hours of ingestion[23]. Similar to studies of stool, the test had excellent sensitivity with detection of ingestion of as little as 25 mg of gluten.

Measuring gluten ingestion and excretion is a paradigm shift which may fundamentally alter the management of patients with celiac disease. The clear advantage of this method is that gluten itself is being measured. Additional potential benefits include broader accessibility to feedback regarding gluten-free diet adherence. For patients, this is akin to the introduction of the sphygmomanometer for patients with hypertension to monitor their own blood pressure or provision of glucometers to patients with diabetes to monitor blood sugar. The availability of accurate information regarding gluten ingestion and, by inference, gluten in foods would greatly enhance the ability of patients with celiac disease to adhere to a strictly gluten-free diet.

D. Design and Methods

(1) Study Design

This is a single-center, investigator initiated study to examine the role of detection of gluten immunogenic peptides (GIPs) in urine and stool in home monitoring of patients with confirmed celiac disease and the impact of this information upon gluten-free diet adherence.

This is a randomized, partially double blind study of the impact of knowledge of diagnostic test results for biomarkers of gluten exposure upon subsequent gluten-free diet adherence, symptoms and quality of life. The 30 week study will involve surveys, home stool and urine collection and additional blood draws as well as three study visits with the study coordinator.

(2) Patient Selection and Inclusion/Exclusion Criteria

Prior to study enrollment, all potential participants will have had a biopsy or serologically/genetically confirmed diagnosis of celiac disease for which the treatment is strict adherence to a gluten-free diet. Patients with confirmed celiac disease who are trying to follow a gluten-free diet will be identified through a chart review of outpatient clinical appointments. The patient's primary GI physician will be contacted to confirm whether they are appropriate to be approached for the study. If the primary GI physician agrees that it is appropriate, then potential eligible participants will be contacted by telephone and notified about the study. If they are interested, then they will be asked for verbal consent to receive sample collection materials and a copy of the consent form. The purpose of the telephone screening is to reduce barriers to participation related to the need for a first morning urine sample and decrease participant burden by reducing the number of study visits required. Patients may also be approached for the first time during their clinic visit if the research team is unable to establish contact with them prior to their scheduled visit. In these instances, participants will be given the option to drop off the samples to BCH at the time of their second visit along with the set of samples collected during weeks 1-8.

Recruitment and written informed consent will occur in conjunction with a scheduled outpatient clinic appointment for follow-up of celiac disease at Boston Children's Hospital. Children with celiac disease who are undergoing diet review with a dietitian after 6 or more months on a gluten-free diet will be approached to participate in this study.

Inclusion criteria

- Age 6 to 18 years at study entry
- Diagnosis of celiac disease based upon either
  (a) Biopsy criteria
    - Marsh 3 lesion and/or villous height:crypt depth ratio (Vh:Cd) < 3 with intraepithelial lymphocytosis; and
    - elevated serum tTG IgA and/or EMA antibodies
  (b) Serologic/genetic (ESPGHAN 2012) criteria
    - Symptoms compatible with celiac disease;
    - Serum tTG IgA > 10 x upper limit of normal for assay;
    - EMA titre elevated on a separate sample; and
    - HLADQ genotype compatible with celiac disease.
- Adherence to a gluten-restricted diet (self-reported) for 6 months or more
- Attending a clinician assessment for celiac disease

Exclusion criteria

- Unable to provide urine and/or stool sample or attend study visits
- English proficiency unsuitable for completion of surveys
- Anuria or oliguria
- Reliance upon commercial gluten-free formulas as primary source of nutrition
- Comorbid condition that in the opinion of the investigator would interfere with the subject's participation in the study or would confound the results of the study

(3) Description of Study Treatments or Exposures/Predictors

Prior to the first recruitment visit, patients who have been identified as eligible for this study will be contacted and informed of the study. If interested, they will be asked to provide verbal consent to receive study materials and collect a urine and an optional stool sample for analysis for biomarkers of gluten-free diet adherence. These samples will be brought to the enrollment visit at which time participants will provide written informed consent and have another opportunity to learn about the study and ask questions. The purpose of the telephone screening is to reduce barriers to participation

related to the need for a first morning urine sample and decrease participant burden by reducing the number of study visits required. Participants who could not be contacted may remain eligible to participate if they are willing to collect the samples at home immediately following their clinical appointment. Participants will complete the enrollment visit in conjunction with a scheduled outpatient clinic appointment. Study activities at this visit which are in addition to routine care will include a short questionnaire with items related to celiac disease symptoms, gluten-free diet adherence and quality of life. Measurement of serum tissue transglutaminase antibodies is currently the standard of care for these patients[20,35]. Additional blood will be collected for this study and stored for testing for other biomarkers of gluten-free diet adherence and nutrition. Participants will also be informed that BCH offers LMX-4 numbing cream at no additional cost for use before blood draws. Participants interested in using or receiving further information on this program will be given information cards during their first visit which detail how to obtain the numbing cream, which can be applied by the participant or their parent in order to reduce discomfort and anxiety surrounding blood draws performed as part of this study.

The next phase of the study will occur primarily at home. During the 7 week run-in phase, participants will collect urine specimens and complete symptom questionnaires at 2 random intervals when prompted by the study co-ordinator. During week 8, there will be a study visit with the research staff. Participants will return samples collected at home along with an additional stool sample collected at week 8 which will be used for randomization to either continued double-blinding to biomarker detection or an open results arm. All participants will have a diet assessment in conjunction with the week 8 study visit. This will occur either in person or remotely by telephone or video link. During the last phase of the study (weeks 8-30), participants will be prompted to collect additional urine specimens and complete questionnaires at random intervals (~q 4 weeks). Participants in the open arm may also collect up to 4 additional stool samples during this time as well.

Participants in the open results arm will also be provided with home testing kits so that they may receive immediate qualitative (yes/no) feedback regarding the presence of biomarkers of gluten exposure in their stool and/or urine. Collection of urine samples will be initiated by the investigators. Collection and testing of stool samples will occur at times of the participants choosing. Participants may opt to test up to 4 stool samples, and will report test use date, results of the test, and reasons for use to the research team after each use.At the end of the 30 week study period, all participants will have a final study visit and an additional diet assessment by a Registered Dietitian. All participants will be unblinded to the results of biomarker testing after their samples have been processed. Blood will be collected and stored for testing of biomarkers of gluten-free diet adherence at the first study visit. If a participant agrees to blood sample collection at their third study visit, blood will also be collected at that time (weeks 0, and 30).

(4) Definition of Primary and Secondary Outcomes/Endpoints

Primary outcomes:

- Difference in frequency of gluten exposure following randomization in blinded vs. open results groups. Gluten exposure is defined as the average per individual subject post-randomization percentage of samples collected between weeks 8 and 30 with detectable gluten immunogenic peptides using the quantitative assay.

Secondary outcomes:

- Difference in mean gluten exposure following randomization in blinded vs. open results groups. Mean gluten exposure is defined as the average per individual subject post-randomization concentration of gluten immunogenic peptides detected using the quantitative assay.
- Per individual change in frequency and quantity of gluten exposure pre- and post-randomization in blinded and open results groups.
- Symptom score (average for weeks 8 through 30 and at week 30) with blinded vs. open results of biomarker detection.

- Symptom score (average during run-in compared to week 30) with blinded vs. open results of biomarker detection.
- Change in celiac disease specific quality of life as measured by CDDUX[36] between weeks 1 and 30 in blinded vs. open results groups.
- Change in health related quality of life between weeks 8 and 30 as measured by PedsQL core 4.0[37] in blinded vs. open results groups.
- Growth trajectory (weight, height and BMI) between weeks 8 and 30.
- Agreement between results of patient/parent performed qualitative testing and quantitative testing performed by research team
- Rate of school absences and missed extracurricular activities in blinded vs. open results group.

(5) Data Collection Methods, Assessments, Interventions and Schedule (what assessments performed, how often)

This randomized, partially double-blinded study will involve three study visits as well as home questionnaires, urine and stool collection, and diet assessment by a Registered Dietitian. The first study visit is in conjunction with a scheduled outpatient clinic appointment for follow-up of celiac disease. There will be additional visits with the study coordinator at randomization (week 8) and study completion (week 30). The interval between the first and second study visits is a run-in period to allow for behavior modification in response to the clinician assessment and/or participation in a study where adherence will be monitored. A dietitian assessment will be conducted by a Registered Dietitian at randomization (week 8) and at the end of the study (week 30). At each study visit, participants/caregivers will be asked to complete symptom and quality of life questionnaires Blood may be collected and stored for testing for biomarkers of gluten-free diet adherence, celiac disease activity and nutrition at the initial and final study visits. Throughout the study period, participants will maintain a diary of suspected and probable gluten exposures.

During weeks 2 through 7 (between the first and second study visits), when prompted by the study co-ordinator, participants will collect their next urine at home and to complete the symptom questionnaire. Participants will be blinded to the exact timing of sample collection. This method will be employed throughout the study period to ensure that sample collection reflects usual behavior and to reduce the Hawthorne Effect due to participants adjusting their eating behaviors in anticipation of observations being collected.

During week 8, participants will bring samples collected at home and completed questionnaires to the second study visit along with an additional stool sample taken at the week 8 time point. At this time, there will be a blood draw and participants will be randomized to continue with double-blinded test results or an open results arm. Randomization will be stratified based upon the results of GIP testing in stool collected at week 8 to ensure that participants with documented gluten exposure are distributed equally between the blinded and open results arms. Participants in the open results arm will receive instruction in using home test kits for detection of GIPs and supplied with test kits to be used at home during the remainder of the study period. Participants will be given a parking voucher and receive a $30 ClinCard as a token of appreciation. All participants will also have a diet assessment by a Registered Dietitian either in person or remotely by telephone or video link in conjunction with the week 8 study visit.

During weeks 8 through 30, participants will keep a diary of any suspected gluten exposures. Participants will be contacted by the study co-ordinator at random intervals (approximately every three to four weeks) and instructed to collect their next urine and complete the symptom questionnaire. Participants in the open results arm will also perform home testing and send a photo of the test results to the study co-ordinator to document results and confirm test completion. Used test kits may be disposed in household trash. Participants will also test up to 4 stool samples during this time that will be collected and tested at the discretion of the participant. Participants will report date of use, results,

and reason for use after each home stool test. Participants will return all other study materials and containers at the final study visit.

At week 30, participants will have a final study visit with the study co-ordinator to return urine samples collected at home. An optional blood draw will be performed for testing for markers of gluten-free diet adherence and celiac disease activity and participants/caregivers will be asked to complete a questionnaire with items pertaining to symptoms and quality of life. All participants will also have a diet assessment by a Registered Dietitian either in person or remotely by telephone or video link in conjunction with the week 30 study visit. Participants will receive a parking voucher and $30 on their ClinCard as a token of appreciation. Participants in the open arm will be instructed to report all unused stool test kits. Participants in the blinded arm will be given up to 4 test kits to keep at this visit as a token of appreciation for completing the study.

All participants will be informed of the results of their urine sample used for stratification at the final study visit. Participants in the blinded arm will be contacted and notified of results of testing for biomarkers of gluten-free diet adherence (GIPs) once this has been completed. Disclosure of test results to treating providers will be at the discretion of participants.

(6) Study Timeline (as applicable)

- Eligibility Screening
    - Participants who are eligible for this study will be identified when they are scheduled for an outpatient clinical appointment for follow-up of celiac disease
    - Potential participants will be contacted and informed of the study. If they express that they may be interested in participating, they will be asked to provide verbal consent to receive sample collection materials and a copy of the consent form.
    - urine sample (from a first morning void if possible) will be collected. Optional stool sample collected.
- Recruitment Visit (week 1) in conjunction with a scheduled outpatient clinic appointment for follow-up of celiac disease
    - written informed consent
    - provide stool and urine samples (may be collected prior to visit)
    - patient/parent self-report questionnaire
    - height and weight
    - blood draw: TTG, DGP, CBC, stored samples for makers of gluten-free diet adherence, celiac disease activity and nutrition.
    - Participant receives a parking voucher
- At home (weeks 1 through 7)
    - collect additional urine samples and complete questionnaire when contacted by study coordinator at random intervals (x2)
    - keep a diary of suspected/probable gluten exposures.
    - collect an additional stool sample during week 8 (to be used at week 8 study visit for randomization)
- Study Visit 2: (week 8)
    - Return samples and questionnaires completed at home when prompted.
    - Bring additional stool sample collected during week 8 (for randomization)
    - Randomization to blinded or open test results.
    - patient/parent self-report questionnaires
    - height and weight
    - Participant receives parking voucher and $30 ClinCard as a token of appreciation
    - Diet assessment, either in person or remotely by telephone or video link
- At home (weeks 8 through 30)
    - collect additional urine samples and complete questionnaire when contacted by study coordinator at random intervals (x6, approximately every four weeks)
    - keep a diary of suspected/probable gluten exposures
    - Use of stool kits at participants discretion (x0-4)

- Final study visit (week 30)
    - Return samples and questionnaires completed at home.
    - Complete quality of life and symptom questionnaires.
    - Diet assessment, either in person or remotely by telephone or video link.
    - Height and weight
    - Optional blood draw: TTG, DGP, CBC, stored samples for makers of gluten-free diet adherence, celiac disease activity and nutrition.
    - Participants informed of results of sample used for stratification.
    - Participant is given parking voucher and $30 ClinCard as a token of appreciation
    - Blinded participants given test kits (x4) as a token of appreciation
- All participants will be unblinded and notified of results once the samples are processed.

E. Adverse Event Criteria and Reporting Procedures

All subjects who participate and have a subsequent safety evaluation will be included in the safety analyses. All adverse events reported during the study will be listed, documenting course, severity, and outcome. Laboratory parameters, vital signs, and physical exam results will be summarized with descriptive statistics as appropriate.

F. Data Management Methods

All study participants will be assigned a unique study identifier which will be used to link all study data (lab results, anthropometrics, questionnaire responses, etc). The master list of subject names and study IDs will be stored and locked in a file cabinet in the research office. Only study staff will have access to this list. All other samples will be labelled with the date, patient initials and study ID number. All labs collected for clinical purposes at the time of study blood draw will be labelled with the patient's name, medical record and DOB, processed per standard procedure through the laboratory department and entered into the medical record as these are clinically relevant to patient care. This will include samples for EMA and TTG at scheduled clinic visits. All other study-related labs will be labelled with the study ID, processed without identifying information and will not be entered into the medical record. All data (lab results, pathology results and survey results) will be indexed using the study ID and collated in a REDCap database administered by Boston Children's Hospital.

G. Quality Control Method

Study investigators will oversee data entry and will follow progress to assure accuracy of the data. All weight and height measurements will be obtained by trained staff. Equipment to measure quantitative levels of GIPs will be calibrated regularly according to the manufacturer protocol.

H. Data Analysis Plan

For all outcomes, descriptive data analysis will be used to assess variables' distributions and to detect outliers and influential observations. We will estimate means (and standard deviations) and medians (and interquartile ranges) of continuous variables, and proportions of categorical variables. In addition, we will examine the data using plots, such as boxplots, histograms and smoothed-scatterplots. When necessary, variables will be transformed to meet assumptions for statistical tests. All statistical tests will be two-sided and will use a Type I error of 5%. For confidence intervals, we will use two-sided 95% coverage probabilities.

As a general approach, all proportions will be reported as mean with the associated 95% confidence interval for the estimate. This will provide more meaningful information about the precision of each estimate as well as the possible clinical significance of any observed differences in the mean value. As such, p values for comparisons of means will not be determined with the implicit assumption that values for which the 95% confidence intervals overlap do not differ significantly. Relationships between continuous measures will be analyzed using Pearson's correlation coefficient. Where appropriate,

continuous measures will also be converted to categorical variables (e.g., serum antibody negative/positive vs. GIP negative/positive).

Primary outcome
For the primary outcome, gluten exposure is defined as percentage of samples collected between weeks 8 and 30 with detectable gluten immunogenic peptides using the quantitative assay. Differences in gluten exposure between the blinded and open results groups will be assessed using the chi-squared test.

Secondary outcomes
Outcomes related to gluten exposure will be considered as continuous variables and also converted to categorical variables. The per individual change in frequency of gluten exposure will be determined by calculating the difference in the proportion of GIP positive urine samples in the pre-randomization (weeks 1, 2, and 4) and post-randomization (weeks 8 through 30) samples. The same visits will be used to calculate the per individual change in mean quantity of gluten exposure pre- and post-randomization. Results will be categorized as decreased, no change or increased frequency/mean concentration of gluten exposure.

Symptom and quality of life scores are also continuous variables and group comparisons will be assessed using a paired t-test. The PedsQL 4.0 Generic Subscales has 23 items across four subscores (physical, emotional, social and school functioning) and scores are scaled to range from 1 to 100. The scale has been validated for children aged 5 to 18 and the minimally clinically important difference (MCID) is 4.4 for child report and 4.5 for parent report. The CDDUX has 12 items and three subscores related to diet, communication and having celiac disease[36]. It is also scaled from 1 to 100 and has been shown to correlate with perceptions of disease severity.

Agreement between results of patient/parent performed qualitative testing and quantitative testing performed by research team will be assessed using McNemer's test (qualitative testing) or intraclass correlation (quantitative testing).

I. Statistical Power and Sample Considerations

The primary outcome is the difference in rate of gluten detection in the six urine samples provided after randomization (weeks 8 through 30) between the blinded and unblinded groups. A total sample of 102 (n=51 in each group) provides 90% power to detect a difference of 50% gluten detection in the blinded group versus 25% gluten detection in the open results group, given six outcomes per participant with an intraclass correlation of 0.6 and alpha set at 0.05. Given a more conservative intraclass correlation of 0.8, we will still have 82% power to detect the predicted effect size. If participants are more highly adherent, then this sample size should also be sufficient as fewer participants will be required. For example, using the same assumptions for intraclass correlation, with 43 subjects in each group there is 90% power to detect a difference of 40% gluten detection in the blinded versus 25% gluten detection in the open results group (alpha = 0.05).

J. Study Organization

This is study will be conducted at a single site (Boston Children's Hospital). Primary oversight will be by Dr Jocelyn Silvester with the support of the co-investigators, Drs Alan Leichtner and Dascha Weir. The research assistant for the Celiac Disease Program will be assigned to this study and responsible for data collection.

K. References

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