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General Information

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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

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Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): NCT00207675 - A Randomized, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Anti-TNF a Chimeric Monoclonal Antibody (Infliximab, REMICADE) in Pediatric Subjects With Moderate to Severe CROHN'S Disease
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

TOWARDS AN IMPROVED PEDIATRIC CROHN'S DISEASE ACTIVITY INDEX: INTEGRATING CLINICAL TRIAL AND REGISTRY DATA TO IDENTIFY KEY DRIVERS OF CHANGE

Narrative Summary:
Crohn's disease is a chronic inflammatory bowel condition that is often diagnosed in childhood. Clinicians often use measures of disease activity such as the Pediatric Crohn's Disease Activity Index (PCDAI), which rates the severity of symptoms on items such as abdominal pain, well-being, blood work lab values, and growth. The current study will be looking at how well the questions on the PCDAI capture disease activity, and will modify the questionnaire based on these findings. The United States Food and Drug Administration (FDA) mandates use of measures like the PCDAI in clinical trials, and as such wants to ensure that it is appropriately capturing disease activity and response to therapy.

Scientific Abstract:
Background: The United States Food and Drug Administration (FDA) is advocating for a redefinition of endpoints used in clinical trials, including the need for patient reported outcomes of disease state. The current study seeks to investigate and redefine the drivers of remission on the Pediatric Crohn's Disease Activity Index (PCDAI), the primary end-point in pediatric Crohn's Disease (CD) clinical trials.
Objective: Identify which elements of the PCDAI are driving and differentiating remission from non-remission.
Study Design: This study will combine data from the REACH trial, the IMAgINE trial, and the Pediatric IBD (PIBD) registry in order to look at which elements of the PCDAI best drive response and predict remission over time.
Participants: Data from 112 patients from the REACH trial, 188 patients from the IMAgINE trial, and 414 patients from the PIBD registry will be combined.
Main Outcome Measure(s): PCDAI, IMPACT-III, lab markers of inflammation.
Statistical Analysis: Descriptive statistics will be used to examine the distribution of patient scores on the individual

PCDAI questions, and subsets of PCDAI questions (e.g., subjective items, lab values). Drivers of change will be determined, and logistic regression will be carried out to determine which PCDAI items best classify patients' disease state. Receiver Operating Characteristic (ROC) curves will be run to propose new clinical endpoints that define response and remission. This will be essential for use in clinical trials in order to define eligibility for studies, and response to therapy.

Brief Project Background and Statement of Project Significance:
To date, the Pediatric Crohn's Disease Activity Index (PCDAI) has been the standard tool in pediatrics to assess disease extent and clinical response to treatment 1. The PCDAI combines outcomes reported by patients (or a proxy such as a caregiver) and a clinician, and also includes growth parameters, and laboratory values. Initial validation of the PCDAI took place with 133 children with CD 1. Subsequently, the PCDAI was validated in four studies of children with CD, demonstrating good psychometric properties 2-6.

Traditionally, endpoints chosen for clinical trials have been based on multi-item indices such as the PCDAI, which can incorporate symptoms, signs, laboratory tests, and endoscopic measures 7. However, there are feasibility issues associated with the use of these multi-item indices, and as such, the United States Food and Drug Administration (FDA) sponsored Gastroenterology Regulatory Endpoints and Advancement of Therapeutics (GREAT) workshops are reassessing their use 7.

The FDA is beginning to redefine endpoints used in clinical trials, based on the need for objective measures of disease state. Although the ultimate goal of this reform is to create and use patient reported outcomes (PROs) to measure clinical trial end-points in addition to other objective measures of disease (e.g.endoscopy) and health related quality of life8, 9, a PRO for pediatric CD disease activity is still in the early stages of development and it will be years before this measure is ready for use in new clinical trials. As such, the FDA has asked several members of the academic and pharmaceutical communities to investigate and redefine the drivers of remission on the PCDAI, most commonly used as the primary end-point in pediatric Crohn's Disease (CD) clinical trials.

There have been other versions of the PCDAI developed, which have increased feasibility: the Abbreviated PCDAI 10-12, the Short PCDAI 12, and the Modified PCDAI 13. However, these versions have lower face, construct and discriminant validity 2. A mathematically weighted version (wPCDAI) was developed. Key features include the removal of 3 items that have shown to be redundant on a multivariable analysis, 2 of low feasibility (height velocity and abdominal examination) and one blood measurement (Hematocrit) 2.

Although the weighted version has demonstrated improvement over the original PCDAI, there are some concerns over excluding height and abdominal exam items (as done on the weighted PCDAI) based on our preliminary analyses (presented at a recent GREAT-III conference) showing that these variables help to identify patients with active disease. These questions were also found to account for a significant proportion of variance in PCDAI change scores over time in response to treatment.

Accurate assessment of response to treatment and disease management are dependent upon valid and reliable measurement of disease activity. Given that the PCDAI is the most frequently used endpoint in pediatric CD clinical trials, the current study is essential to advance scientific knowledge and come to a consensus on the best available questions needed to assess disease activity in pediatric IBD.

Specific Aims of the Project:
In the past 6 months, the investigators involved in the proposed research have begun work to examine drivers of change on the PCDAI through a national registry dataset—the pediatric Inflammatory Bowel Disease (PIBD) registry. This work was carried out, and presented alongside similar analyses by the pharmaceutical companies involved with the REACH trial (pediatric CD trial of infliximab)14, and the IMAgINE trial (pediatric CD trial of adalimumab)15. The goal of the current proposal is to:
1. Access and merge the relevant variables from these three datasets in order to derive more conclusive results regarding the components of the PCDAI that contribute to remission and response to therapy.
2. Develop a new version of the PCDAI that best characterizes disease activity in pediatric CD.
3. Propose new endpoints for this measure to be used in future pediatric CD clinical trials.

Based on preliminary analyses, the PCDAI items of abdominal pain, stool frequency, and well-being are the primary drivers of change with evidence towards the inclusion of one to two lab values, and growth in long-term assessments of change. The proposed research will increase the power of the analyses, and will use the same approach to reach a consensus on which PCDAI items to include.

What is the purpose of the analysis being proposed? Please select all that apply. Other

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
We are requesting access to the REACH dataset through this data request. We currently have access to the PIBD Registry dataset, and will also be requesting access to the IMAgINE dataset, as previously described.

There will be no specific exclusion criteria, however, we will restrict analyses to those patients who have complete PCDAI data at each respective time point. As such, we are requesting participant level data on all available participants in the REACH dataset.

Main Outcome Measure and how it will be categorized/defined for your study:
The main outcome measure is the individual questions that comprise the current Pediatric Crohn's Disease Activity Index (PCDAI). Both individual questions will be examined in terms of their contribution to explaining response and remission, as well as groups of questions that best explain response/remission. As such, a new version of the PCDAI will be created, for which psychometric properties and new endpoints will be defined. In order to carry out these analyses, we will need participant-level data on each individual PCDAI item, at each time point it was completed. This index has previously defined endpoints and definitions of response to therapy. However, these will be reexamined and redefined through this study.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
There is no independent variable that will be examined in terms of a predictive relationship to our primary outcome measure. However, change on the PCDAI or elements of the PCDAI will be examined in relation to other measures of disease state including Global Assessments of Change (Physician, Parent, Patient), and a pediatric disease-specific measure of health related quality of life completed by patients—the IMPACT-III, completed in both the PIBD registry and the REACH datasets. The IMPACT-III asks participants about some of their symptoms (e.g., How much has your stomach been hurting you in the past two weeks? Response range: Not very much, to Not at all), and the degree to which they impair daily functioning. We will compare a subjective patient-reported measure to a clinician reported measure of disease state, on some aspects of disease activity. We will look at correspondence between patient-physician and/or parent-physician scores to further understand response and disease state.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
We may describe therapy type or concomitant medication use in order to define the sample, but will not be directly examining these variables in relation to disease activity, or response to therapy. We will also require access to demographic data (e.g., age, gender, disease extent, disease location) in order to describe the sample and possibly examine any confounding variables.

We will not be looking to reexamine response to treatment, and thus will not require access to information around randomization to treatment.

Statistical Analysis Plan:
Statistical analysis will consist of the following:
1. Descriptive statistics (Percentages, Means) to describe the baseline symptom characteristics of children newly diagnosed with CD will be run.
2. We will look at the distribution of patient scores on each PCDAI question.
3. Scores for subjective items (Abdominal pain, Stooling pattern, Patient well-being), Lab values (Hematocrit, Erythrocyte Sedimentation Rate, and Albumin), and other indicators of disease state (Weight, Height, Abdominal Tenderness, Perirectal disease, and Extra-intestinal manifestations) will be examined together to look at distribution of scores, and redundancy of items.
4. Drivers of change, in other words, which questions on the PCDAI change more in response to therapy, will be examined.
5. Once drivers of change are identified, we will further examine this change through linear regression. This will show the percentage of variance in scores accounted for by each of the PCDAI questions. This may further identify redundancy or removal of items.

6. Logistic regression will be carried out to look at different PCDAI models in order to determine the best combination of variables that correctly classify response and remission.
7. Psychometric properties of the newly proposed instrument will be examined and compared to previous PCDAI versions.
8. Lastly, Receiver Operating Characteristic (ROC) curves will be run to propose new clinical endpoints that establish cutoff values to define response and remission. This will be essential for use in clinical trials in order to define eligibility for studies, and ultimately response to therapy.

Project Timeline:
Since the FDA would like to begin using less subjective measures of disease state as soon as possible, this work will be carried out within a fairly short timeline.

Proposed start date: As soon as data is available; Estimated by July 2015.
Analysis completion date: January, 2016.
Date 1st manuscript draft submitted for publication: March, 2016.
Results reported back to the YODA Project: 1 year from date that data is provided by REACH and IMAgINE, Estimated to be July 2016.

Dissemination Plan:
This work will be presented at both North American and European conferences on IBD (e.g., North American Society for Gastroenterology and Nutrition, European Society for Gastroenterology and Nutrition), and will be submitted for publication in a high tier, widely disseminated peer-reviewed journal (e.g., Gastroenterology, Inflammatory Bowel Diseases, The American Journal of Gastroenterology) within the next year.

Bibliography:
[1] Hyams JS, Ferry GD, Mandel FS, Gryboski JD, Kibort PM, Kirschner BS, et al. Development and Validation of a Pediatric Crohn's Disease Activity Index. Journal of Pediatric Gastroenterology and Nutrition. 1991;12:439-47.
[2] Turner D, Griffiths AM, Walters TD, Seah T, Markowitz J, Pfefferkorn M, et al. Mathematical weighting of the pediatric Crohn's disease activity index (PCDAI) and comparison with its other short versions. Inflammatory Bowel Diseases. 2012;18:55-62.
[3] Kundhal PS, Critch JN, Zachos M, Otley AR, Stephens D, Griffiths AM. Pediatric Crohn disease activity index: responsive to short-term change. Journal of Pediatric Gastroenterology and Nutrition. 2003;36:83-9.
[4] Otley A, Loonen H, Parekh N, Corey M, Sherman PM, Griffiths AM. Assessing activity of pediatric Crohn's disease: which index to use? Gastroenterology. 1999;116:527-31.
[5] Hyams J, Markowitz J, Otley A, Rosh J, Mack D, Bousvaros A, et al. Evaluation of the pediatric Crohn disease activity index: a prospective multicenter experience. Journal of Pediatric Gastroenterology and Nutrition. 2005;41:416-21.
[6] Turner D, Griffiths AM, Walters TD, Seah T, Markowitz J, Pfefferkorn M, et al. Appraisal of the pediatric Crohn's disease activity index on four prospectively collected datasets: recommended cutoff values and clinimetric properties. The American Journal of Gastroenterology. 2010;105:2085-92.
[7] Levesque BG, Sandborn WJ, Ruel J, Feagan BG, Sands BE, Colombel JF. Converging Goals of Treatment for Inflammatory Bowel Disease, from Clinical Trials and Practice. Gastroenterology. 2014.
[8] Matza LS, Patrick DL, Riley AW, Alexander JJ, Rajmil L, Pleil AM, et al. Pediatric patient-reported outcome instruments for research to support medical product labeling: Report of the ISPOR PRO good research practices for the assessment of children and adolescents task force. Value in Health. 2013;16:461-79.
[9] Ruemmele FM, Hyams JS, Otley A, Griffiths A, Kolho KL, Amil Dias J, et al. Outcome measures for clinical trials in paediatric IBD: an evidence-based, expert-driven practical statement paper of the paediatric ECCO committee. Gut. 2014.
[10] Loonen HJ, Griffiths AM, Merkus MP, Derkx HH. A critical assessment of items on the Pediatric Crohn's Disease Activity Index. J Pediatr Gastroenterol Nutr. 2003;36:90-5.
[11] Shepanski MA, Markowitz JE, Mamula P, Hurd LB, Baldassano RN. Is an abbreviated Pediatric Crohn's Disease Activity Index better than the original? Journal of Pediatric Gastroenterology and Nutrition. 2004;39:68-72.
[12] Kappelman MD, Crandall WV, Colletti RB, Goudie A, Leibowitz IH, Duffy L, et al. Short pediatric Crohn's disease activity index for quality improvement and observational research. Inflammatory Bowel Diseases. 2011;17:112-7.
[13] Leach ST, Nahidi L, Tilakaratne S, Day AS, Lemberg DA. Development and assessment of a modified pediatric Crohn disease activity index. Journal of Pediatric Gastroenterology and Nutrition. 2010;51:232-6.
[14] Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, Johanns J, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology.

2007;132:863-73; quiz 1165-6.
[15] Hyams JS, Griffiths A, Markowitz J, Baldassano RN, Faubion WA, Jr., Colletti RB, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. Gastroenterology. 2012;143:365-74 e2.