**Investigator Initiated Sponsored Research (IISR) Protocol Guide for Clinical Studies**

IISR is defined as unsolicited, independent research where the investigator or the institution (academic, private, or governmental) serves as the Sponsor and Takeda provides support in the form of study drug and/or funding.

IISR proposals are reviewed by Takeda medical and scientific personnel. Decisions are based upon scientific merit as well as alignment with research areas of interest and availability of resources.

Support for an IISR is awarded strictly based on research merit criteria. Support of a study in no way implies any obligation toward or is any way connected to the recommendation or prescribing of Takeda products.

THIS IS AN INSTRUCTIONAL PAGE FOR THE PROTOCOL GUIDE PLEASE REMOVE PRIOR TO SUBMITTING

Black text = Mandatory text. Please do not delete nor edit.  
Blue text = Instructions/guide. Please update with study specific information.  
Items marked <> need to have the specified item added

Items marked give options for recommended/required text

**Information to be included with the protocol submission:**

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| **General information:**   * Requestor information (name, email, phone) * Investigator information (name, institution email, phone, institution, address, CV) * Country(s) where study will be conducted * Product(s) * Study title * Study duration (number months, estimated start and end dates – inclusive of projected enrollment) * Resources requested (study drug and/or funding) * Study Type ( i.e. clinical interventional, non-interventional, observational) | **Protocol content:**   * Background & rationale * Study objectives * Inclusion/exclusion criteria * Study design/schedule (including # of subjects and sites, treatments/procedures) * Study drug * Study endpoints * Study duration * Safety reporting plan * Statistical analysis plan * Data management plan * Publication plan * References * Detailed budget |
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**IISR submissions can be made via the web at** [www.takeda.com/research/iisr](http://www.takeda.com/research/iisr)

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| **IISR GUIDE (to be completed in English)**  **STUDY INFORMATION**  **Date: (*DD/MM/YY)***  **Protocol Version:** | |
| **Country(s) the study will be conducted in:** | The United stages |
| **Compound/Product :** | no |
| **Study Type :** | Observational study |
| **Study Title:** | **A Pilot Survey of Inflammatory Bowel Disease Patients on Health Insurance Satisfaction** |
| **Indication:** | Gastroenterology |

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| **INVESTIGATOR CONTACT INFORMATION** | |
| **Number of Sites:** | One |
| **Principal Investigator Contact:** |  |
| *Principal Investigator Name* | Peter D.R. Higgins |
| *Organization Name* | Division of Gastroenterology, University of Michigan |
| *Address* | Taubman Center, Floor 3, Reception D  1500 E Medical Center Dr  Ann Arbor, MI, 48109 |
| *Telephone* | 734-647-2964 |
| *Fax* | 734.763.2535 |
| *E-mail address* | phiggins@med.umich.edu |
| **Co or Sub-Investigator(s) Contact (if applicable):** |  |
| *Sub-Principal Investigator Name* | Julajak Limsrivilai |
| *Organization Name* | Division of Gastroenterology, University of Michigan |
| *Address* | Taubman Center, Floor 3, Reception D  1500 E Medical Center Dr  Ann Arbor, MI, 48109 |
| *Telephone*  *Fax*  *E-mail address* | 734-764-4758  734.763.2535  jlimsriv@med.umich.edu |
| **Study Assistant(s)/Coordinator(s) Contact:** |  |
| *Name (address, phone number, email)* | Amber Elder |
| **Institution’s Contracts or Grants office contact:** |  |
| *Name (address, phone number, email)* |  |
| **Name and contact information of person completing this form:**  *(name, address, phone number, email)* | Julajak Limsrivilai  Division of Gastroenterology, University of Michigan  734-764-4758  jlimsriv@med.umich.edu |

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| **RESOURCES REQUESTED** | |
| **Resource Requested:** | Funding |
| **Estimated Study Budget:**  *(Enter total here – including direct, indirect cost and institutional overhead)* | $7,480 |
| **Do you have additional funding sources for this project?** | No. |
| **Dosage and Formulation:** | None. |
| **Estimated Total Drug Supply for Study:** | None. |
| **Total # of Subjects:** | 2,000 estimated participants |
| **Study Timeline:**  *Planned Study Activation: (month/year)*  *Study activation is final regulatory authority approved protocol and fully executed contract* | *2 months* |
| *Study Activation to First Patient In (days, weeks, months):* | *1 week* |
| *First Patient In to Last Patient In*  *(days, weeks, months)* | *14 months* |
| *Last Patient In to Last Patient Out (days,weeks, months)* | *Same day* |
| *Monthly enrollment rate: (days)* | *1,000 patients per month* |
| *Treatment duration:* | *None.* |
| *Number of Study Sites/Depots:* | *One* |
| *Completion of Data Analysis:* | *16 months* |
| *Completion of Final Study Report/Manuscript: (month/year)* | *18 months* |
| *Publication Plan:* | *The American Journal of Gastroenterology* |

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| **STUDY PROPOSAL** |
| **Background and rationale:**  Patients with chronic diseases, including Inflammatory Bowel DIsease (IBD), often have difficulty with obtaining and maintaining adequate health insurance in the multipayer US health insurance market. When IBD patients shop for health insurance (generally each autumn), there is remarkably little data on customer satisfaction, health insurance ratings, or even what is covered at different levels of monthly payment and annual deductible. IBD patients are not informed consumers, and often find themselves regretting their insurance purchase decisions, which are locked in for one year.  Unfortunately, switching insurers is also problematic, as insurers use multiple policies to limit benefits, especially drug benefits for expensive biologic medications, to new policyholders and their families. This often results in gaps in coverage, and gaps in maintenance of use of biologic therapies. This is particularly problematic, as unlike small molecule therapies, gaps in biologic use can lead to increased rates of antibody formation, and loss of response to a biologic medication. Since many IBD patients are diagnosed before age 30, and often live 50 years or more with IBD, they can “burn through” the limited number of biologic medications available rather quickly.  In order to obtain an accurate picture of IBD patient satisfaction with US health care insurance, we performed a pilot survey of self-reported IBD patients with a Google Forms survey. Our eventual goal is to improve our initial survey with a series of small pilots, then scale this project up to a survey through CCFA Partners of their 14,000 patient cohort of IBD patients. We hope to identify insurance factors that affect overall IBD patient satisfaction with healthcare insurance in the US, after controlling for confounding patient factors. We hope that IBD patients will be able to use this information in shopping for and selecting health insurance that will best suit their needs. |
| **Hypothesis:** |
| There may be some insurance factors that affect overall IBD patient satisfaction with healthcare insurance in the US. |
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| **Primary Aim/Objective:**  To identify insurance factors that affect overall IBD patient satisfaction with healthcare insurance in the US, after controlling for confounding patient factors |
| **Secondary Aim/Objective:** none |
| **Primary Endpoint(s):** |
| The response from IBD patients to questionnaires |
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| **Secondary Endpoint(s):** None |
| **Study Plan:**  Using a Google Forms survey and posts on Twitter, we recruited a convenience sample of self-identified IBD patients following Amber Elder (@ColitisNinja) or Peter Higgins (@ibddoctor) on Twitter. Respondent characteristics and insurer characteristics were collected between 5/30/2015 and 6/12/2015 with 48 respondents. Preliminary data analysis was done. Overall satisfaction was considered as the primary outcome. We found some independent factors associated with overall satisfaction such as disabled status, receiving denied payment for a medication in the past year, coverage difficulty for any IBD medication, and coverage difficulty for anti-TNF therapy. This preliminary analyses supported our hypothesis; however, these based on very small number of respondents. In addition, some questions in the questionnaire did not have clear meaning. The survey with larger number of respondents and improved questionnaire is warranted. We have edited our questionnaire (see below). we plan to do a pilot study with 1,000 patients in Crohn's & Colitis Foundation of America (CCFA) partners to validate the usability and accuracy of the questionnaire. Finally, we plan to survey 14,000 IBD patients in CCFA partners.  **Questionnaire**  PLEASE NOTE: ALL OF YOUR ANSWERS SHALL REMAIN ANONYMOUS. THE PURPOSE OF THIS POLL IS TO GAIN INFORMATION ONLY!  1.Which form of IBD have you been diagnosed with? \*   * Please check one.   + Crohn's Disease   + Ulcerative Colitis   + Indeterminate Colitis   2. How many health insurances do you currently have?  3.Who is your current health insurance plan with?   * Please choose the main one.   + Humana Group   + UnitedHealth Group   + Anthem Group (formerly Wellpoint, Inc. Group)   + Aetna Group   + Celtic   + Assurant   + Select Health   + Kaiser Foundation Group   + Cigna Health Group   + Coventry   + HCSC Group   + Highmark Group   + Blue Shield of California Group   + Independence Blue Cross Group   + Centene Corp Group   + HIP Insurance Group   + BCBS of New Jersey Group   + BCBS of Michigan Group   + Guidewell Mutual Holdings Group   + California Physician's Group   + Wellcare Group   + Carefirst Inc. Group   + Health Net of California Group   + Molina Healthcare Group   + UHC of California   + Lifetime Healthcare Group   + BCBS of Massachusetts Group   + Metropolitan Group   + Cambia Health Solutions Group   + None of these. My health coverage is handled through a health share based company.   + Other:   Please choose your other insurances  (same insurance choices as above)  4. How many times in the last 2 years that you have changed insurance?  5. How long have you used your current insurer?  6. If you have used your current insurance for less than 1 year, please specify your previous insurance company.  (same insurance choices as above)  7. Are you the policy holder of your health insurance? \*   * + Yes, I am.   + No, I am not.   + I'm not sure.   8.How many people are covered under your current health insurance?  (How many people in your household are covered? Include spouse/partner and children.)  9.What is your monthly insurance payment?  (Example: If your monthly payment is $200 dollars, type in, "$200".   * This includes both your own payment and your employer payment * If the amount is in range, please input the maximum value) * € I don’t know   10.What is your estimated annual deductible? (deductible = a specified amount of money that you must pay before an insurance company will pay a claim.)  (Example: If your deductible is $1500 dollars, type in "$1500".   * If the amount is in range, please input the maximum value. * Input “0” if you have no deductible.)   € I don’t know  11.Approximately how much out-of-pocket was spent last year? (out-of-pocket = money you have to pay adding on the insurance company pay, and not include deductible)  (Give your best estimation of how much you spent last year.  If the amount is in range, please input the maximum value.  Input “0” if you don’t have to pay more from the bill covered by insurance company.)   * 12. How many times have you had surgery in the past year?   Please give your best estimation.   * 13. How many times were you treated at an ER in the past year?   Please give your best estimation.   * 14. How many times have you been hospitalized in the past year?   Please give your best estimation.   * 15. How many endoscopies and colonoscopies total have you had in the past year?   Please give your best estimation.  (Count the total number of procedures. For example, if you underwent both upper endoscopy and colonoscopy within the same session, please count as 2 procedures.)   * 16. What strategies have you seen insurance companies use to make it more difficult to get medications paid for? * 17. Does your insurance company cover biologic medications (e.g., Remicade, Simponi, Cimzia, Entyvio, Humira)? \*   + Yes   + No   + Not Applicable * 18.If you answered "No," please explain your experience. * 19.Does your insurance forced switch of your biologic medications?   + Yes   + No   20. If yes, which biologics your insurance company preferred? (can select > 1 choice)   * + Remicade   + Humira   + Cimzia   + Simponi   + Entyvio   21.Did you use a company assistance program/copay program?   * + Yes   + No   22.Has your insurance company denied payment for other medications that your physician has prescribed? \*   * + Yes   + No   23. What tips or tricks can you share with other people living with IBD who need help in working with insurance carriers to receive benefits?  24.How would you rate the overall service of your insurance company for IBD patients?   * If not applicable, please skip to next question.   25.Please rate your difficulty getting IBD medications covered.   * If not applicable, please skip to next question.   26. Please rate your difficulty getting anti-TNF biologics covered.   * If not applicable, please skip to next question.   27. Please rate your difficulty getting Entyvio covered.   * If not applicable, please skip to next question.   28. Would you recommend this type of health insurance to other IBD patients?   * + Yes   + No   29. If you have ever been on a biologic, have you ever had a gap in your treatment because of insurance?   * + Yes   + No   + Not sure   + Not Relevant (I have never been on a biologic)   30. If your answer to the question No.29 is “yes”, how long was the gap?  \_\_\_\_\_\_\_\_\_\_\_ months \_\_\_\_\_\_\_\_\_\_\_weeks  31. If your answer to the question No.29 is “yes”, which biologic did you have a gap for?    32. If your answer to the question No. 29 is "yes," please explain why:   * Check all that apply.   + denial (after previous approval)   + slow approval/prior authorization   + slow or no annual renewal   + gap when I changed insurance companies   + Other:   33. If you checked "other," please explain.  34.Did you develop antibodies to the biologic because this gap in your medication coverage?   * + Yes   + No   + Not Applicable   35. Before or during the gap were you on an immunomodulator like Imuran or methotrexate?   * + Yes   + No   + :   36. Would you be interested in viewing the results from this poll?   * + Yes   + No   37. What is your average yearly household income?   * + Less than $25,000   + $25,000 - $34,000   + $35,000 - $49,999   + $50,000 - $79,999   + $80,000 - $100,000   + Over $100,000   38. If you are under 26 years of age, are you on your parents' insurance plan?   * Please choose one. * Yes No * Please choose one of the following:   + currently working   + not working by choice   + disabled   + unable to find work   39. What state do you live in? |
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| **Safety Reporting (please do not change the safety section of the template)**  *Institution/Investigator is solely responsible for reporting all Adverse Events and Serious Adverse Events to regulatory authorities, investigators, IRBs or IECs and Takeda, as applicable, in accordance with national regulations in the countries where the study is conducted.*  *Regardless of expectedness or causality, all SAEs and pregnancy reports must also be reported in English by facsimile to Takeda Pharmacovigilance or designee:*  ***Fatal and Life Threatening SAEs*** *within 24 hours of the sponsor-investigator’s observation or awareness of the event*  ***All other serious (non-fatal/non life threatening) events*** *within 4 calendar days of the sponsor-investigator’s observation or awareness of the event*  ***Takeda Safety Reporting Contact Information***  ***Takeda requires that all information be communicated to Takeda’s Pharmacovigilance Department as outlined in the study contract.***  *All reported adverse drug reactions and safety issues related to Takeda compound must be included in the final study report.*  *Describe procedures for reporting Adverse Events and Serious Adverse Events.*  ***Definitions:***  *Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a medicinal product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.*  *An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.*  *An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. This includes adverse reactions which arise from: use of a medicinal product within the terms of the marketing authorization; use outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors; and occupational exposure\*.*  *\* This corresponds to the exposure to a medicinal product for human use as a result of one’s occupation, such as nurses who may handle products routinely in their occupational setting.*  *Serious AE (SAE) means any untoward medical occurrence that at any dose:*   * *Results in* ***death.*** * *Is* ***life-threatening*** *(refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).* * *Requires inpatient* ***hospitalization or prolongation of an existing hospitalization*** *.* * *Results in* ***persistent or significant disability or incapacity****. (Disability is defined as a substantial disruption of a person’s ability to conduct normal life functions).* * *Is a* ***congenital anomaly/birth defect****.* * *Is a* ***medically important event****. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.*   *An IMPORTANT MEDICAL EVENT also includes any event described in Takeda Medically Significant AE List below:*   |  |  | | --- | --- | | *Acute respiratory failure/acute respiratory distress syndrome* | *Anaphylactic shock* | | *Torsade de pointes/ventricular fibrillation/ventricular tachycardia* | *Acute renal failure* | | *Malignant hypertension* | *Pulmonary hypertension* | | *Convulsive seizures* | *Pulmonary fibrosis* | | *Agranulocytosis* | *Confirmed or suspected endotoxin shock* | | *Aplastic anemia* | *Confirmed or suspected transmission of infectious agent by a medicinal product* | | *Toxic epidermal necrolysis/Stevens-Johnson syndrome* | *Neuroleptic malignant syndrome/malignant hyperthermia* | | *Hepatic necrosis* | *Spontaneous abortion/stillbirth and fetal death* | | *Acute liver failure* |  |   *Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient’s life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.* *Procedures for Reporting Drug Exposure during Pregnancy and Birth Events* *If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form to the Takeda Pharmacovigilance or designee immediately. The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Takeda Pharmacovigilance or designee will request this information from the sponsor-investigator. Please refer to study contract for Takeda pharmacovigilance contact information.*  *If a female partner of a male patient becomes pregnant during the male patient’s participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Takeda Pharmacovigilance or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome. Please refer to study contract for Takeda pharmacovigilance contact information.* *Product Complaints and Medication Errors*  *A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Takeda and report the event.*  *A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact Takeda (see below) and report the event.*  ***Phone: 1-877-TAKEDA7 (1-877-825-3327)***  ***E-mail:*** [***medicalinformation@tpna.com***](mailto:medicalinformation@tpna.com)  ***FAX: 1-800-247-8860***  *Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to Takeda Pharmacovigilance.* |
| **Statistical Analysis:**  *Study Design/Description* – crossectional study  *Accrual and Feasibility* – we want to survey 14,000 IBD patients in CCFA partner. We anticipate the accrual rate of 1000 respondents per month.  *Efficacy Analysis.*  Patient demographics were collected and reported as percentages, means, or medians (if skewness > 2x the standard error of the skewness).  Univariate analyses of patient and insurance predictors of these outcomes were analyzed with chi square (categorical variables) or t-test (continuous variables) statistics. For continuous variables with significant skewness, the Mann-Whitney U test was used. Data were exported from Google Forms as a csv file, and were analyzed in R 3.1.2. |
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| **Data Management Plan:** |
| Clinical records for all participants studied will be maintained by at UNC in a secure storage facility for a minimum of five years following study completion. After this time, related paper will be destroyed in a secure manner. Electronic data will be retained in the same manner as during the study – in password-protected files kept in a secure, locked location. |
| **Ethical and Regulatory Considerations:**  *Prior to initiating the study, the Investigator must obtain written approval to conduct the study from appropriate institutional ethical and/or regulatory committee and send a copy to Takeda (gma.externalresearch@takeda.com). Should changes to the study become necessary, copies of written approvals from appropriate institutional ethical and/or regulatory committees must be sent to Takeda (gma.externalresearch@takeda.com).*  *If research involves human subjects, the Investigator must register the study with clinical trials.gov and other appropriate entities, as necessary.*  *An IND or CTA may be required. The investigator is responsible to work with regulatory authority to obtain or prove exemption* |
| **References:**  There has been no study about this issue up to now |
| ***Supporting documentation/tables and graphs:***  None. |
| **Detailed Budget for all study related costs:**  1. Subject selection   * List $1,000.00   2. Module implementation   * Long module, Moderate complexity $4,500.00   3. Data extraction   * Data extraction and statistical analysis $1,000.00 * Statistical analysis 0.00   4. Other   * Project Management 300.00   **Total payable to CCFA partners $6,800.00**  CCFA DATABASE ACCESS FEES (billed by and payable to CCFA)  10% of direct project costs **total $680.00** |