Comparative Effectiveness of Biologic or Small Molecule Therapies after Failure of Anti-TNF Treatment in Patients with Crohn's Disease and Ulcerative Colitis

NCT number NCT04852666
Document Date 05/01/2019

Study Protocol*

Initial study protocol included additional studies that are not part of this clinicaltrials.gov submission. These additional studies have been removed from this version of the protocol we are submitting to clinicaltrials.gov. No other changes have been made to the protocol.

May 1, 2019

Comparative Effectiveness of Biologic or Small Molecule Therapies after Failure of Anti-TNF Treatment in Patients with Crohn's Disease and Ulcerative Colitis

A. SPECIFIC AIMS

Crohn's disease (CD) and ulcerative colitis (UC), collectively referred to as inflammatory bowel disease (IBD), affect approximately 1.2 million individuals in the United States[1], cost over $6 billion annually[2], and cause substantial patient morbidity[3,4], missed work[5] and school[6], and diminished quality of life.[7,8] Currently anti-TNF therapy is considered first line treatment for moderate to severe disease. [9-13] Yet, primary non-response occurs in up to 30% of patients and secondary loss of response is observed in up to 80% of patients.[14,15]

When anti-TNF therapy fails, subsequent treatment options for CD include vedolizumab (α4 β7 integrin antibody) and ustekinumab (anti-IL-12/23 antibody). For UC, options include vedolizumab or tofacitinib (small molecule JAK inhibitor with anticipated FDA approval for UC around 3/2018[16]). Unfortunately, anti-TNF refractory patients respond less well to subsequent treatments,[17-21] underscoring the importance of selecting the most effective 2nd line agent. Yet, there is a paucity of comparative effectiveness research (CER) to guide this challenging clinical decision faced my many patients and their providers.[22,23] Given the expanding therapeutic armamentarium in IBD, the Institute of Medicine, Crohn's & Colitis Foundation (the Foundation), and others have prioritized CER research to guide treatment algorithms.[24-26]

The overarching aim of this project is to compare the effectiveness of non-anti-TNF biologics and small molecules after failure of anti-TNF therapy. We propose to address this pressing, unmet need for CER in IBD with a series of complementary prospective and retrospective cohort studies and through the linkage of PCORnet Health Plan Research Networks (HPRNs) with the CCFA Partners Patient Powered Research Network (PPRN). We will also leverage an existing multi-center clinical cohort sponsored by the Foundation. Through the use of these varied sources of real-world data, our study findings will be broadly generalizable [27] and directly inform these important patient treatment decisions.

Aim 1: To compare the effectiveness of second line biologic agents (vedolizumab versus ustekinumab) among patients with Crohn's disease (CD) who are anti-TNF primary or secondary non-responders.

We will perform a prospective cohort study through the recruitment and linkage of participants from our HPRN Partners (HealthCore and Humana) with the CCFA Partners PPRN, and by leveraging an existing multi-center cohort. Outcomes will include disease specific and general patient reported outcomes (PROs) 26 weeks following treatment initiation.

Aim 2: To compare the effectiveness of a second line biologic agent (vedolizumab) versus small molecule (tofacitinib) among patients with ulcerative colitis (UC) who are anti-TNF primary or secondary non-responders.

We will perform parallel prospective cohort study in UC as described for CD above.

B. BACKGROUND

Crohn's disease (CD) and ulcerative colitis (UC), collectively referred to as inflammatory bowel disease (IBD), affect approximately 1.2 million individuals in the U.S.[1] and cost over $6 billion annually[2]. Typical symptoms (e.g., abdominal pain, bloody diarrhea)[28] result in substantial morbidity including,[3,4] missed work[5] and diminished quality of life.[7,8]

The primary treatment goals for all IBD patients are to 1) induce remission by eradicating intestinal inflammation and related symptoms and, 2) maintain remission by preventing disease flares and progression. In 1998, the FDA approval of infliximab, the first anti-tumor necrosis factor (TNF) biologic agent, revolutionized the treatment landscape for IBD. More recently, a number of additional anti-TNF and other biologics have been FDA-approved.[28]

Currently anti-TNF treatment is considered first line therapy for patients with moderate to severe disease.[9-13] However, primary non-response occurs in up to 30% of patients and secondary loss of response is observed in up to 80% of

patients.[14,15] Fortunately, the therapeutic armamentarium continues to grow. When anti-TNF therapy fails, subsequent treatment options for CD include vedolizumab (α4 β7 integrin antibody) or ustekinumab (anti-IL-12/23 antibody). For UC, options are vedolizumab or tofacitinib (small molecule JAK inhibitor with anticipated FDA approval in March 2018).[16]

Unfortunately, anti-TNF refractory patients respond less well to subsequent treatments[17-21], underscoring the importance of selecting the most effective 2nd line agent. This is a *high-risk/ high-reward treatment decision,* requiring patients and their physicians to weigh the potential benefits of these new treatments (improved symptoms and quality of life, halting disease progression, and modifying disease course) against severe, life-threatening short- and long-term risks (serious infectious and malignancy). Yet, there is a paucity of patient-centered comparative effectiveness research

C. Study Design

This comparative effectiveness project comprises two prospective cohorts (CD and UC) and two retrospective cohorts (CD and UC). Each prospective cohort will be a secondary data analysis of data collected through two external cohort studies (IBD Partners and SPARC-IBD). The retrospective cohort studies will utilize health care claims data from HealthCore and Humana, analyzed through the PCORnet distributed research network (Coordinating Center, Harvard Pilgrim).

C.1 Existing Resources and Study Settings

IBD Partners is an internet-based cohort study of patients living with CD and UC. Participants complete a baseline survey, and receive follow-up surveys every 6 months. Surveys are designed to collect discrete data using a variety of formats including radio buttons and/or drop-down menus. This allows for real-time implementation of range and consistency checks, and greatly reduces missing data. To the extent possible, survey items are based on validated instruments and include assessments of medication adherence, exercise, disease symptoms and activity, and QOL/PRO measurements. Measures that are both general (NIH PROMIS) and disease-specific (disease activity indices and QOL measures). Participants can also update their treatment and outcome information on an "on demand" basis on our patient portal.

Participant recruitment and follow-up in the IBD Partners study is ongoing. To facilitate recruitment of patients initiating treatment with vedolizumab, ustekinumab, and tofacitinib, we have partnered with the research divisions leading health plans (HealthCore/Anthem and Humana) to identify new users of these medications and invite them to join the cohort. To encourage retention of such patients, we have created customized email notifications and will be providing a $25 incentive to participants who complete a follow-up survey 4-10 months after initiating one of these treatments of interest.

In addition to survey data, for participants recruited by the health plans, we will obtain a patient-level dataset derived from claims data that includes basic demographics along with indicators of the following: diagnoses/comorbidities, medication use, and basic measures of health services utilization (hospitalization, surgery, endoscopy) before and after index date.

Study of Prospective Clinical Adult Research Cohort (SPARC) is a prospective, multi-center cohort of adult IBD patients with longitudinal collection of clinical and patient-reported data and biosamples. Clinical and demographic characteristics of all participants are captured at the time of enrollment and updated during follow-up visits and hospitalizations. Data elements include disease phenotype, duration of disease, selected laboratory data, prior surgeries, and prior medication use. Data on validated endoscopic severity scores are also captured.[33,37] Most clinical data are captured at the point of care through an EHR-based "Smartform" at each site, and subsequently extracted, transformed, and loaded (ETL) into the I2B2-based Plexus data warehouse. This clinical data is supplemented by PROs collected quarterly through electronic surveys.

C.2 Prospective Cohort Studies

Crohn's disease

Study Population. *Inclusion criteria* will include 1) diagnosis of CD, as reported by the participant (PPRN) and/or treating physician (SPARC); 2) initiation of either ustekinumab or vedolizumab (date of the first dose, as reported by the participant or recorded in the medical record in SPARC, will be considered the index date); 3) age ≥ 18 years; and 4) treatment with anti-TNF prior to index date.

Comparators. As above, new users of ustekinumab or vedolizumab

Outcomes. Co-primary outcomes will be NIH Patient Reported Outcome Measurement and Information System (PROMIS) measures of Pain Interference and Fatigue, which have been prioritized by our patient co-investigators and PPRN Patient Governance Committee. PROMIS scales are continuous measures, calibrated using a T-score metric to the US general population with a mean of 50 and standard deviation of 10. Minimal important differences (MIDs) are in the range of 2 to 6[41]. Our primary outcomes will be measured approximately 6 months following treatment initiation. We will use available surveys completed 4-10 months from the index date of qualifying medication, selecting the survey closest to 6 months.

Secondary PROs which may include a disease-specific symptom index (Short Crohn's Disease Activity Index)[32] and l PROMIS Social Satisfaction.

Statistical Analysis . We will first describe characteristics of new initiators of each treatment, and compare mean PROMIS T-scores (approximately 6 months after treatment initiation) for Pain Interference and Fatigue. We will then utilize generalized linear mixed models (GLMM) to compare outcomes by treatment group, taking into account clustering by sub-cohort (internal PPRN population, referral from HPRN, and SPARC-IBD), and adjusting for the following covariates of interest: age, gender, race/ethnicity, time from diagnosis (< 2 or ≥ 2 years), smoking status, body mass index (BMI) baseline disease activity disease as measured Short Crohn's Disease Activity Index[32], other baseline indicators of health status such as the PROMIS domains listed above, prior use of corticosteroids and other immune suppressive agents (e.g. azathioprine, mercaptopurine, methotrexate, cyclosporine, tacrolimus prior to index date), and ongoing use of concomitant immune suppression.

In addition, each sub-cohort offers the opportunity to evaluate a unique set of expanded covariates. For example, existing PPRN participants will have rich data about health behaviors (i.e. Godin-Shephard Leisure-Time Physical Activity Questionnaire[42] and the Patient Activation Measure[43]). HPRN-referred participants will have data on healthcare utilization and data on comorbidities included in the Deyo-Charlson Comorbidity Index (DCCI)[44] and a validated, IBD specific severity score.[45,46] SPARC participants will have an expanded array of clinical data including anatomic location of disease, endoscopic severity, body mass index (BMI), and selected laboratory values (ESR, CRP, hemoglobin, albumin).

We will first conduct separate analyses of each population using each sub-cohort's full data extent, and will report sub-cohort-specific estimates of the treatment effects, with 95% confidence intervals (CI). Next, we will compare the covariate characteristics that were measured in each sub-cohort (enumerated in the above paragraph); if those common covariates suggest similar patient populations across sub-cohorts, then we will assess heterogeneity of treatment effects (HTE) in the full data. If treatment effect estimates from the full data suggest homogeneity, then we will report the results from the GLMM as described above.

Missing data: Missing data may occur due to either loss to follow up and/or incomplete responses to survey items. We will make every possible effort to monitor and mitigate against this risk of missing data, and will report on the occurrence of drop-out and summarize results on all patients in the prospective cohort. We will use multiple imputation[47] to account for missing data, based on the assumption that data will be missing at random conditional on the joint distribution of an extensive set of covariates measured on each participant. We will also perform sensitivity analyses to assess the robustness of findings to plausible alternative assumptions about the missing data.[48]

Pre-specified subgroup analyses and Heterogeneity of Treatment Effects. All analyses will be stratified by time from diagnosis (< 2 or ≥ 2 years), number of prior anti-TNF therapies, age group (18 to <40, 40 to <65, >65), sex, and use of concomitant immune suppressive therapy. For each subgroup analysis, we will estimate treatment effects and 95% CIs within each subgroup, and graphically display results across subgroups. Although the study will not have adequate power for each subgroup analysis, estimating the effect size and precision will provide useful hypothesis-generating data.

Sample size and Power. Our sample size is based upon the co-primary outcomes of this analysis, PROMIS measures of Pain Interference and Fatigue, which will be assessed approximately 6 months after treatment initiation. We estimate our needed sample size on the following assumptions:

- The threshold of a clinically relevant effect size is a difference in mean T scores of ≥ 5. This is based on prior longitudinal data from our CCFA Partners network indicating that a change of 5 points is associated with "improvement" or "worsening" of disease activity. [34] In addition, MIDs for these PROMIS measures in other

conditions have been estimated between 3 and 6.[49] If the true treatment difference falls below this threshold, then other factors such as type of dosing (oral, subcutaneous, intravenous), dosing interval (daily, weekly, monthly) will play a more important role in treatment decisions.

- Based on our preliminary data, the ratio of patients exposed to each treatment may be as high as 2:1
- Loss to follow up rate may be as high as 20%

Based on the above, a total of 180 participants will be needed to achieve 80% power with a two-sided α of 0.05.

Ulcerative colitis

Our UC prospective cohort will be parallel in design to the CD cohort described above, with the following minor changes.

Study population. *Inclusion criteria* will include 1) diagnosis of UC, as reported by the participant (PPRN) and/or treating physician (SPARC); 2) initiation of either tofacitinib or vedolizumab. Other eligibility criteria will remain the same.

Outcomes will remain the same with the substitution of a self-reported UC symptom index.[33]

Sample size and recruitment potential. As with the CD cohort, our required sample size is 180 participants.

D. References

1. Kappelman MD, Moore KR, Allen JK, Cook SF. Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured US population. *Digestive diseases and sciences.* Feb 2013;58(2):519-525.
2. Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. *Gastroenterology.* Dec 2008;135(6):1907-1913.
3. Vernier-Massouille G, Balde M, Salleron J, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. *Gastroenterology.* Oct 2008;135(4):1106-1113.
4. Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology.* Oct 2008;135(4):1114-1122.
5. Longobardi T, Jacobs P, Bernstein CN. Work losses related to inflammatory bowel disease in the United States: results from the National Health Interview Survey. *Am J Gastroenterol.* May 2003;98(5):1064-1072.
6. Ferguson A, Sedgwick DM, Drummond J. Morbidity of juvenile onset inflammatory bowel disease: effects on education and employment in early adult life. *Gut.* May 1994;35(5):665-668.
7. Cohen RD. The quality of life in patients with Crohn's disease. *Aliment Pharmacol Ther.* Sep 2002;16(9):1603-1609.
8. Akobeng AK, Suresh-Babu MV, Firth D, Miller V, Mir P, Thomas AG. Quality of life in children with Crohn's disease: a pilot study. *J Pediatr Gastroenterol Nutr.* Apr 1999;28(4):S37-39.
9. Gomollon F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis.* Jan 2017;11(1):3-25.
10. Dassopoulos T, Sultan S, Falck-Ytter YT, Inadomi JM, Hanauer SB. American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF-alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. *Gastroenterology.* Dec 2013;145(6):1464-1478 e1461-1465.
11. Harbord M, Eliakim R, Bettenworth D, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. *Journal of Crohn's and Colitis.* 2017.
12. Dassopoulos T, Cohen RD, Scherl EJ, Schwartz RM, Kosinski L, Regueiro MD. Ulcerative Colitis Care Pathway. *Gastroenterology.* Jul 2015;149(1):238-245.
13. Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. *Gastroenterology.* May 2015;148(5):1035-1058 e1033.

14. Billioud V, Sandborn WJ, Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. *Am J Gastroenterol.* Apr 2011;106(4):674-684.
15. Karmiris K, Paintaud G, Noman M, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology.* Nov 2009;137(5):1628-1640.
16. Pfizer's sNDA for Xeljanz Ulcerative Colitis Treatment Accepted by FDA. (https://www.pharmpro.com/news/2017/07/pfizers-snda-xeljanz-ulcerative-colitis-treatment-accepted-fda). accessed 09/03/2017.
17. Feagan BG, Rubin DT, Danese S, et al. Efficacy of Vedolizumab Induction and Maintenance Therapy in Patients With Ulcerative Colitis, Regardless of Prior Exposure to Tumor Necrosis Factor Antagonists. *Clin Gastroenterol Hepatol.* Feb 2017;15(2):229-239 e225.
18. Sands BE, Sandborn WJ, Van Assche G, et al. Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease in Patients Naive to or Who Have Failed Tumor Necrosis Factor Antagonist Therapy. *Inflamm Bowel Dis.* Jan 2017;23(1):97-106.
19. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. *New England Journal of Medicine.* 2016;375(20):1946-1960.
20. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology.* Feb 2012;142(2):257-265.
21. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. *New England Journal of Medicine.* 2017;376(18):1723-1736.
22. Peyrin-Biroulet L, Lopez A, Sandborn W. Head-to-head Comparative Studies: Challenges and Opportunities? *J Crohns Colitis.* Mar 01 2017;11(suppl_2):S567-S575.
23. Ungaro RC, Colombel JF. Editorial: biologics in inflammatory bowel disease—time for direct comparisons. *Alimentary Pharmacology & Therapeutics.* 2017;46(1):68-69.
24. Hart AL, Lomer M, Verjee A, et al. What Are the Top 10 Research Questions in the Treatment of Inflammatory Bowel Disease? A Priority Setting Partnership with the James Lind Alliance. *J Crohns Colitis.* Feb 2017;11(2):204-211.
25. Denson LA, Long MD, McGovern DP, et al. Challenges in IBD research: update on progress and prioritization of the CCFA's research agenda. *Inflamm Bowel Dis.* Mar-Apr 2013;19(4):677-682.
26. Bray J, Fernandes A, Nguyen GC, et al. The Challenges of Living with Inflammatory Bowel Disease: Summary of a Summit on Patient and Healthcare Provider Perspectives. *Can J Gastroenterol Hepatol.* 2016;2016:9430942.
27. Jarow JP, LaVange L, Woodcock J. Multidimensional Evidence Generation and FDA Regulatory Decision Making: Defining and Using "Real-World" Data. *JAMA.* Aug 22 2017;318(8):703-704.
28. Hutfless S, Almashat, S, Berger Z, Wilson LM, Bonson E, Chen Q, Donath E, Herlong F, Puhan MA, Selvaraj S, Tuskey A, Vasilescu A, Bass EB, Worthington M, Palamaner G, Lazarev M. Pharmacologic Therapies for the Management of Crohn's Disease: Comparative Effectiveness. Comparative Effectiveness Review No. 131. (Prepared by Johns Hopkins Evidence-based Practice Center under Contract No. 290-2007-10061-I.) AHRQ Publication No. 14-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
29. Eden J, Wolman D, Greenfield S, Sox H. *Initial National Priorities for Comparative Effectiveness Research.* Institute of Medicine, National Academies Press; 2009.
30. AGA policy statement on comparative effectiveness research. American Gastroenterological Association; 2010.
31. Hutfless S, Lau BD, Wilson LM, Lazarev M, Bass EB. Pharmacological Management of Crohn's Disease: Future Research Needs. Future Research Needs Paper No. 26. (Prepared by the Johns

Hopkins University Evidence-based Practice Center under Contract No. 290-2007-10061-I.) AHRQ Publication No. 13(14)-EHC017-EF. Rockville, MD: Agency for Healthcare Research and Quality. February 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

32. Thia K, Faubion WA, Jr., Loftus EV, Jr., Persson T, Persson A, Sandborn WJ. Short CDAI: development and validation of a shortened and simplified Crohn's disease activity index. *Inflamm Bowel Dis.* Jan;17(1):105-111.

33. Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis.* Dec 2008;14(12):1660-1666.

34. Kappelman MD, Long MD, Martin C, et al. Evaluation of the patient-reported outcomes measurement information system in a large cohort of patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* Aug 2014;12(8):1315-1323 e1312.

35. Gaines LS, Slaughter JC, Horst SN, et al. Association Between Affective-Cognitive Symptoms of Depression and Exacerbation of Crohn's Disease. *Am J Gastroenterol.* Jun 2016;111(6):864-870.

36. Ananthakrishnan AN, Long MD, Martin CF, Sandler RS, Kappelman MD. Sleep disturbance and risk of active disease in patients with Crohn's disease and ulcerative colitis. *Clin Gastroenterol Hepatol.* Aug 2013;11(8):965-971.

37. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc.* Oct 2004;60(4):505-512.

38. McAuliffe ME, Lanes S, Leach T, et al. Occurrence of adverse events among patients with inflammatory bowel disease in the HealthCore Integrated Research Database. *Current medical research and opinion.* 2015;31(9):1655-1664.

39. Liu J, Sylwestrzak G, Ruggieri AP, DeVries A. Intravenous Versus Subcutaneous Anti-TNF-Alpha Agents for Crohn's Disease: A Comparison of Effectiveness and Safety. *Journal of managed care & specialty pharmacy.* Jul 2015;21(7):559-566.

40. Sylwestrzak G, Liu J, Stephenson JJ, Ruggieri AP, DeVries A. Considering patient preferences when selecting anti-tumor necrosis factor therapeutic options. *American health & drug benefits.* Apr 2014;7(2):71-81.

41. Shalhoub H, Reaney M. *PROMIS® tools as endpoints in clinical trials: what should you know? A review of PROMIS® capabilities and the current regulatory space.* Vol 32016.

42. Amireault S, Godin G, Lacombe J, Sabiston CM. The use of the Godin-Shephard Leisure-Time Physical Activity Questionnaire in oncology research: a systematic review. *BMC medical research methodology.* 08/12 10/30/received 07/06/accepted 2015;15:60.

43. Hibbard JH, Stockard J, Mahoney ER, Tusler M. Development of the Patient Activation Measure (PAM): Conceptualizing and Measuring Activation in Patients and Consumers. *Health Services Research.* 2004;39(4 Pt 1):1005-1026.

44. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *Journal of Clinical Epidemiology.*57(12):1288-1294.

45. Ananthakrishnan AN, McGinley EL, Binion DG, Saeian K. A novel risk score to stratify severity of Crohn's disease hospitalizations. *Am J Gastroenterol.* Aug 2010;105(8):1799-1807.

46. Ananthakrishnan AN, McGinley EL, Binion DG, Saeian K. Simple score to identify colectomy risk in ulcerative colitis hospitalizations. *Inflamm Bowel Dis.* Sep 2010;16(9):1532-1540.

47. DB R. *Multiple Imputation for Nonresponse in Surveys.* New York, New York: Wiley; 1987.

48. Little RJ, D'Agostino R, Cohen ML, et al. The Prevention and Treatment of Missing Data in Clinical Trials. *New England Journal of Medicine.* 2012;367(14):1355-1360.

49. Yost KJ, Eton DT, Garcia SF, Cella D. Minimally important differences were estimated for six PROMIS-Cancer scales in advanced-stage cancer patients. *Journal of clinical epidemiology.* 2011;64(5):507-516.

50. Ray WA. Evaluating Medication Effects Outside of Clinical Trials: New-User Designs. *American Journal of Epidemiology.* 2003;158(9):915-920.

51. Gagne JJ, Han X, Hennessy S, et al. Successful Comparison of US Food and Drug Administration Sentinel Analysis Tools to Traditional Approaches in Quantifying a Known Drug-Adverse Event Association. *Clinical pharmacology and therapeutics.* Nov 2016;100(5):558-564.

52. Zhou M, Wang SV, Leonard CE, et al. Sentinel Modular Program for Propensity Score-Matched Cohort Analyses: Application to Glyburide, Glipizide, and Serious Hypoglycemia. *Epidemiology.* Nov 2017;28(6):838-846.

53. King G, Nielsen R. Why Propensity Scores Should Not Be Used for Matching.

54. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology.* Jul 2009;20(4):512-522.

55. Rassen JA, Glynn RJ, Brookhart MA, Schneeweiss S. Covariate selection in high-dimensional propensity score analyses of treatment effects in small samples. *Am J Epidemiol.* Jun 15 2011;173(12):1404-1413.

56. Sturmer T, Rothman KJ, Glynn RJ. Insights into different results from different causal contrasts in the presence of effect-measure modification. *Pharmacoepidemiology and drug safety.* Oct 2006;15(10):698-709.

57. Normand ST, Landrum MB, Guadagnoli E, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol.* Apr 2001;54(4):387-398.

58. Kurth T, Walker AM, Glynn RJ, et al. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. *Am J Epidemiol.* Feb 1 2006;163(3):262-270.

59. Sturmer T, Rothman KJ, Avorn J, Glynn RJ. Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution--a simulation study. *Am J Epidemiol.* Oct 1 2010;172(7):843-854.

60. Lund JL, Richardson DB, Sturmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Current epidemiology reports.* Dec 2015;2(4):221-228.

61. Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology.* Mar 1976;70(3):439-444.

62. Sturmer T, Glynn RJ, Rothman KJ, Avorn J, Schneeweiss S. Adjustments for unmeasured confounders in pharmacoepidemiologic database studies using external information. *Med Care.* Oct 2007;45(10 Supl 2):S158-165.

63. Sturmer T, Schneeweiss S, Avorn J, Glynn RJ. Adjusting effect estimates for unmeasured confounding with validation data using propensity score calibration. *Am J Epidemiol.* Aug 1 2005;162(3):279-289.

64. Sturmer T, Schneeweiss S, Rothman KJ, Avorn J, Glynn RJ. Performance of propensity score calibration--a simulation study. *Am J Epidemiol.* May 15 2007;165(10):1110-1118.

65. Office of Rare Diseases Research. *http://rarediseases.info.nih.gov/gard/9856/pediatric-crohns-disease/resources/1, accessed on October 21, 2014.*

66. Brookhart MA, Stürmer T, Glynn RJ, Rassen J, Schneeweiss S. Confounding control in healthcare database research: challenges and potential approaches. *Medical care.* 2010;48(6 0):S114-S120.

67. Harvard Research Data Security Policy Level 4 Requirements. *http://security.harvard.edu/filebrowser/HRDSPLevel4requirements10110.pdf, Accessed on September 25, 2013.*

68. University of North Carolina Information Security Policy. *http://its.unc.edu/files/2012/03/ccm1_033440.pdf. Accessed on September 25, 2013.*