AbbVie Data Sharing
Approved Research Proposals

This is a summary of the approved research proposals with executed Data Sharing Agreements that AbbVie received between January 1, 2014 and July 19, 2018, under the Principles of Responsible Clinical Trial Data Sharing. Details of approved research proposals received after July 19, 2018 are maintained on Vivli.

Requests for studies within the scope of the PhRMA/EFPIA Principles are for clinical trials in patients for medicines and indications approved in both the United States (US) and the European Union (EU). Requests for studies beyond the scope of the PhRMA/EFPIA were for products that were not approved in either one or both the US and EU.

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Within scope of the PhRMA/EFPIA principles

Proposal 2015-01

Title of the proposed research
Retracing compliance patterns from blood samples: a comparison with medication event monitoring system recordings.

Primary researcher
Fahima Nekka, Ph.D.

Affiliation
Université de Montréal, Quebec, Canada

Data sharing agreement date
22 April 2015

Research background/rationale
Outpatient use of medication often deviates from the prescribed dose regimen. This may impact the efficacy and toxicity of such medication. We developed a probabilistic method that allows retrieving how patients have used the drug during the few days preceding the collection of blood samples. The performance of the method was evaluated using simulated data only. In order to assess its performance in realistic settings, we plan on applying the method using clinical data. If the method proves both valid and efficient, this would allow: 1) utilization in ambulatory settings: improved medical knowledge on the potential cause of symptoms in patients consulting in external clinics or in those who are hospitalized, from running simple blood tests and 2) utilization in clinical studies by adjusting biased parameter estimates when medication events were not monitored during the data collection period.

Research objectives

- To evaluate the performance of a probabilistic method meant to retrieve the pattern of medication compliance from blood samples. The performance will be assessed by comparing the method's output with recordings from the medication event monitoring system (MEMS).
- To improve the performance of the method by testing various blood sampling strategies from the study's blood sample data points. Investigate how patient characteristics could be used to narrow down the method's uncertainty in retrieved compliance patterns.

Requested study
Study M99-056: A Randomized Open-Label Study of 800mg ABT-378/200 mg Ritonavir QD in Combination with Stavudine and Lamivudine vs. 400 mg ABT-378/100 mg Ritonavir BID in Combination with Stavudine and Lamivudine in HIV-Infected Antiretroviral Naïve Subjects.

Funding source of research
FRSQ – Fonds de la recherché en Santé Québec

Potential conflicts of interest
None

Statistical analysis plan
The SAP report has been provided here.

Publication citation
The results of this research will not be published in a scientific/biomedical or peer reviewed journal. A summary report has been provided here.

Proposal 2015-02

Title of the proposed research
Assessment of intermediate clinical endpoints from studies of clinically localized prostate cancer to identify a reliable surrogate of overall survival benefit

Primary researcher
Christopher Sweeney, MBBS

Affiliation
Dana-Farber Cancer Institute and Harvard Medical School

Data sharing agreement date
30 Nov 2015

Research background/rationale
The conduct of adjuvant therapy trials for clinically localized prostate cancers at high risk of relapse is hampered by requiring an endpoint of overall survival, resulting in a waiting period of 10 to 15 years for enough events to occur and final results to be made available. As such, it is highly desirable to identify an intermediate clinical endpoint in cancer of the prostate (ICECaP) that is a robust surrogate for overall survival. The conduct of adjuvant therapies in a more expeditious manner with earlier “read outs” will more rapidly determine whether the therapies which prolong overall survival in castration resistant prostate cancer (CRPC) decrease the number of patients who relapse and die of prostate cancer when used as adjuvant to prostatectomy or radiation. Agents active in the most resistant state of CRPC may eradicate less resistant disease (hormone sensitive micrometastatic disease) in the adjuvant setting and decrease the number of men who die of prostate cancer. from running simple blood tests and 2) utilization in clinical studies by adjusting biased parameter estimates when medication events were not monitored during the data collection period.

Research objectives

- Identify intermediate clinical endpoints that are surrogates for overall survival when assessing the efficacy of localized prostate cancer therapy
- Identify intermediate clinical endpoints that are surrogates for disease -specific survival and metastatasis-free survival. Perform health economic analysis to model the “cost” savings (cancer burden and treatment) from intensive treatment for high-risk patients up front for 2 years to prevent (eg) 20% relapsing and needing 5 to 10 years of chronic expensive study.

Requested study
Study C94-011: Randomized, comparative study of 3 months versus 8 months of Neoadjuvant combination therapy with Lupron® Depot® and Euflex® prior to radical Prostatectomy in localized prostate cancer.

Funding source of research
Prostate Cancer Foundation, Astellas, Sotio, Millenium-Takeda, and Sanofi

Potential conflicts of interest
Several, none of my relationships impact with work being done as part of the ICECaP effort

Statistical analysis plan
Not available.

Publication citation
The data request was withdrawn by the researcher after the data sharing agreement was signed. No study publication will be provided for this request.

Proposal 2015-03

Title of the proposed research
Towards an improved Pediatric Crohn's Disease Activity Index: Integrating clinical trial and registry data to identify key drivers of change.

Primary researcher
Dr. Anthony Otley

Affiliation
Dalhousie University/IWK Health Centre

Data sharing agreement date
03 Dec 2015

Research background/rationale
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. The PCDAI was validated in four studies of children with CD, demonstrating good psychometric properties. However, there are feasibility issues associated with the use of multi-item indices such as the PCDAI, 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. Accurate assessment is 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 CD.

Research objectives
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), and the IMAgINE trial (pediatric CD trial of adalimumab). 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.

Requested study
Study M06-806: A Multicenter, Double-blind Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects with Moderate to Severe Crohn's Disease

Funding source of research
No current funding.

Potential conflicts of interest
Several: Part of an advisory board for pharma, principle investigator or investigator in the last 3 years, received funding/grant from pharma.

Statistical analysis plan
The SAP report has been provided here.

Publication citation
DOI: 10.3748/wjg.v27.i30.5100

Proposal 2015-06

Title of the proposed research
Efficacy of biologic drugs in short-duration versus long-duration inflammatory bowel disease

Primary researcher
Shomron Ben-Horin, M.D.

Affiliation
Sheba Medical Center, Tel-Aviv University

Data sharing agreement date
27 April 2016

Research background/rationale
Background & aim: The chronic relapsing-remitting course of Crohn's disease (CD), with ensuing bowel damage, is believed to be responsible for a possible reduced rate of response to anti-TNF in patients with long disease duration, as reported in some studies. However, no systematic analysis of all available clinical trials was hitherto performed to examine the correlation of CD duration with response to anti-TNF, or with the response to any biologic drug in general. Moreover, only scant data is available pertaining to such possible correlation in ulcerative colitis (UC). The aim of the present study is to perform a meta-analysis of all published randomized placebo-controlled clinical trials of anti-TNF and anti-integrin agents in IBD, to analyze if there is a correlation between the rate of response to treatment and the duration of disease at treatment initiation.

Anticipated outcome: It is widely believed that early CD responds better to biologic therapy, mostly due to observational studies and/or post-hoc analyses of clinical trials. However, to the best of our knowledge, there is hitherto no systematic meta-analysis examining the association of disease duration in CD with the efficacy of biologic treatment. Moreover, data pertaining to impact of disease

duration on response to biologics is even more scant in UC. Thus, the hereby proposed meta-analysis will provide important and novel systematic insight about the correlation between IBD disease duration and response to biologic therapy. Such information may prove to have important and wide impact on the choice of therapeutic strategies for IBD patients and in particular for decisions regarding top-down versus step-up approaches

Research objectives

- To investigate if the duration of CD or UC is associated with rate of response to biologic therapy

Requested studies
M02-404: A Multi-Center Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects With Crohn's Disease

M05-769: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab Endoscopy Trial to Evaluate the Effects on Mucosal Healing in Subjects With Crohn's Disease Involving the Colon

M04-729: A Multi-Center, Randomized, Double-blind, Placebo-controlled Study of Adalimumab for the Induction of Clinical Remission in Japanese Subjects With Crohn's Disease

M06-837: A Multi-Center, Randomized, Double-blind, Placebo-controlled Study of Adalimumab for the Maintenance of Clinical Remission in Japanese Subjects With Crohn's Disease

M02-433: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Maintenance of Clinical Remission in Subjects With Crohn's Disease

M10-447: A Multi-Center, Randomized, Double-Blind, Placebo-controlled Study of Adalimumab in Japanese Subjects With Moderately to Severely Active Ulcerative Colitis.

M06-826: A Multicenter, Randomized, Double-blind Placebo-controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects With Moderately to Severely Active Ulcerative Colitis

M06-827: A Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects With Moderately to Severely Active Ulcerative Colitis

M02-403: A Phase II Study of the Human Anti-TNF Antibody Adalimumab for the Induction of Clinical Remission in Subjects With Crohn's Disease

M04-691: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects With Moderate to Severe Crohn's Disease Who Have Lost Response or Are Intolerant to Infliximab

Funding source of research
None

Potential conflicts of interest
Several: Consulting to pharmaceutical (pharma) company, Advisory board/steering committee member for pharma company, honorarium from pharma company, principal investigator & Investigator for clinical studies.

Statistical analysis plan
Not available

Publication citation
This research request was transitioned to the Vivli.org data sharing platform. The final publication from this proposal will be posted on Vivli.org.

Proposal 2015-07

Title of the proposed research
PROMIS/FACIT Fatigue in Rheumatoid Arthritis

Primary researcher
David Cella, M.D.

Affiliation
Northwestern University, Chicago IL

Data sharing agreement date
08 June 2016

Research background/rationale
This research will identify changes in Fatigue among RA patients who are undergoing treatment/therapy.

Research objectives

- Evaluate changes in Fatigue among RA patients during treatment.

Requested studies
M04-648: Humira Efficacy Response Optimization Study in Subjects With Active Rheumatoid Arthritis (HERO)
M06-810: A Multicenter, Randomized, Double-Period, Double − Blind Study to Determine the Optimal Protocol for Treatment Initiation With Methotrexate and Adalimumab Combination Therapy in Patients With Early Rheumatoid Arthritis (OPTIMA)
DE020: A Multi-Center Continuation Study of the Human Anti-TNF Antibody D2E7 Administered as a Subcutaneous Injection in Patients With Rheumatoid Arthritis

Funding source of research
NIH 1U2CCA186878-01

Potential conflicts of interest
Several: Consulting to pharmaceutical (pharma) company, advisory board/steering committee member for pharma company, Honorarium from pharma company, principle investigator and investigator for clinical studies and my organization receives funding from a pharma company.

Statistical analysis plan
Not available

Publication citation
This research request was transitioned to the Vivli.org data sharing platform. The final publication from this proposal will be posted on Vivli.org.

Proposal 2016-01

Title of the proposed research
Use of TNF antagonist therapies with or without steroids for induction in Crohn's disease: A Meta-analysis

Primary researcher
Jean-Frederic Colombel, M.D.

Affiliation
Mount Sinai Hospital, New York, United States

Data sharing agreement date
27 December 2016

Research background/rationale
Biologic agents, such as TNF antagonists, and corticosteroids are highly effective for induction of remission in Crohn's disease (CD) and ulcerative colitis (UC). Examination of data from a recent randomized controlled trial of combination therapy in patients with active CD suggests that the addition of corticosteroids to infliximab may result in higher remission rates.

Research objectives

- Our objective is to perform a meta-analysis of existing induction trials of biologic therapies to assess whether adjunctive therapy with corticosteroids results in greater efficacy than biological monotherapy.
- A secondary objective is to compare the safety of the two strategies.

Requested study
M02-403: A Phase II Study of the Human Anti-TNF Antibody Adalimumab for the Induction of Clinical Remission in Subjects With Crohn's Disease

M02-404: A Multi-Center Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects With Crohn's Disease

M02-433: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Maintenance of Clinical Remission in Subjects With Crohn's Disease

M04-691: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects With Moderate to Severe Crohn's Disease Who Have Lost Response or Are Intolerant to Infliximab

M05-769: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab Endoscopy Trial to Evaluate the Effects on Mucosal Healing in Subjects With Crohn's Disease Involving the Colon

M06-837: A Multi-Center, Randomized, Double-blind, Placebo-controlled Study of Adalimumab for the Maintenance of Clinical Remission in Japanese Subjects With Crohn's Disease

Funding source of research
None

Potential conflicts of interest
Act as a Consultant for Pharmaceutical Company, Participate in Strategic Advisory Role for Pharmaceutical Company and Principle Investigator on Clinical studies.

Statistical analysis plan
The SAP report has been provided here

Publication citation
DOI: https://doi.org/10.1016/j.cgh.2020.06.036

Proposal 2016-02

Title of the proposed research
Comparative efficacy of biologics in resolving extra intestinal manifestations of inflammatory bowel disease: a systematic review and meta-analysis

Primary researcher
Purna C. Kashyap, MBBS

Affiliation
Mayo Clinic, Rochester, United States

Data sharing agreement date
19 January 2017

Research background/rationale
Extra intestinal manifestations (EIMs) are relatively common in patients suffering from inflammatory bowel disease (IBD), of which Crohn's disease (CD) and ulcerative colitis (UC) are the main entities. Some of the most common EIMs have been demonstrated to affect the quality of life in patients with IBD and can even be associated with more comorbidity than the bowel disease itself. Therefore, an early and proper management of EIMs is essential for improving the overall quality of life in patients with IBD.

The importance of developing more specific guidelines for the management of IBD with associated EIMs stems from the fact that some of these inflammatory manifestations can lead to irreversible deterioration and long-term disability if not treated early and effectively. Determining which of the currently available biologic therapies, if any, is the most effective option for managing patients with IBD complicated by EIMs will lead to long-term improvements in quality of life and significant reductions in long term morbidity. We therefore propose a systematic review and meta-analysis of

randomized controlled trials to assess the comparative efficacy of biologics in treating EIMs associated with IBD.

Research objectives

- The primary aim of the study is to assess the comparative efficacy of currently available biologics in resolving EIMs of IBD.
- To compare the results on the efficacy of biologics in resolving musculoskeletal manifestations from trials targeting spondyloarthropathies vs. the results from trials targeting IBD luminal inflammation as a way to evaluate the reliability of the assessments performed in IBD trials.

Requested study
M02-403 (CLASSIC-I): A Phase II Study of the Human Anti-TNF Antibody Adalimumab for the Induction of Clinical Remission in Subjects with Crohn's Disease

M02-404 (CHARM): A Multi-Center Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects with Crohn's Disease

M02-433 (CLASSIC II): A Multi-Center Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Maintenance of Clinical Remission in Subjects with Crohn's Disease

M03-606: A Phase 3 Multicenter Study of the Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Active Ankylosing Spondylitis

M03-607: A Phase 3 Multicenter Study of the Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Active Ankylosing Spondylitis

M04-691 (GAIN): A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects with Moderate to Severe Crohn's Disease Who Have Lost Response or Are Intolerant to Infliximab

M04-729: A Multi-Center, Randomized, Double-blind, Placebo-controlled Study of Adalimumab for the Induction of Clinical Remission in Japanese Subjects with Crohn's Disease

M05-769 (EXTEND): A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab Endoscopy Trial to Evaluate the Effects on Mucosal Healing in Subjects with Crohn's Disease Involving the Colon

M06-826: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the induction of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis

M06-827: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis

M06-837: A Multi-Center, Randomized, Double-blind, Placebo-controlled Study of Adalimumab for the Maintenance of Clinical Remission in Japanese Subjects with Crohn's Disease

M10-447: A Multi-Center, Randomized, Double-Blind, Placebo-controlled Study of Adalimumab in Japanese Subjects with Moderately to Severely Active Ulcerative Colitis

M10-883: A multicenter Study of the Efficacy and Safety of the Human Anti-TNF Mono-colonal Antibody Adalimumab in Subjects with Peripheral Spondyloarthritis

M11-991: A Phase 3, Randomized, Double-Blind, Placebo Controller, Multicenter, Efficacy and Safety Study of Adalimumab in Adult Chinese Subjects with Active Ankylosing Spondylitis

Funding source of research
None

Potential conflicts of interest
Principle Investigator on a Clinical Trial

Statistical analysis plan
Not available

Publication citation
This research request was transitioned to the Vivli.org data sharing platform. The final publication from this proposal will be posted on Vivli.org.

Proposal 2016-03

Title of the proposed research
Interventions for fatigue in inflammatory bowel disease

Primary researcher
Dr. Dawn Farrell, Ph.D., BSc(Hons), PGDTLHE, DipHSMgmt, RGN

Affiliation
University College Cork, Cork, Ireland

Data sharing agreement date
16 August 2017

Research background/rationale
Inflammatory bowel disease (IBD) represents a group of chronic, progressive, complex inflammatory disorders of the digestive tract and approximately five million people have a diagnosis of IBD worldwide. Crohn’s disease (CD) and ulcerative colitis (UC) are the two most common forms of IBD. Individuals with CD or UC experience a wide range of symptoms including diarrhea, abdominal pain, fatigue, weight loss and rectal bleeding. Fatigue has been identified as one of the most burdensome symptoms experienced by individuals with IBD.

Despite the high prevalence of chronic fatigue in IBD, this subjective complaint remains largely ignored in the IBD literature, particularly regarding the investigation of underlying mechanisms and treatment strategies for fatigue. Fatigue has been difficult to delineate due to the subjective nature of

the symptom. In chronic diseases, with consideration given in the context of IBD, fatigue has been defined as a ‘persistent, overwhelming sense of tiredness, weakness or exhaustion resulting in a decreased capacity for physical and mental work.'

Healthcare professionals have identified the need for more information and education to facilitate the management of fatigue in clinical practice. However, the effectiveness of interventions for fatigue in IBD has not been systematically reviewed. It is therefore proposed to systematically review and synthesize existing evidence on the effects of interventions for fatigue in individuals with IBD.

Research objectives
The aim of this review is to assess the efficacy and safety of interventions for fatigue in IBD.

Requested study
M02-404: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects with Crohn's Disease

Funding source of research
Cochrane Collaboration - Fellowship

Potential conflicts of interest
Investigator for clinical studies

Statistical analysis plan
Not available

Publication citation
This research request was transitioned to the Vivli.org data sharing platform. The final publication from this proposal will be posted on Vivli.org.

Proposal 2017-02

Title of the proposed research
The impact of patient global assessment in the definition of remission as a predictor of long-term radiographic damage and physical function in patients with Rheumatoid Arthritis: an individual patient data meta-analysis

Primary researcher
José António Pereira da Silva, M.D.

Affiliation
Centro Hospitalar e Universitario de Coimbra, Coimbra, Portugal

Data sharing agreement date
5 July 2017

Research background/rationale
Disease remission or low disease activity (LDA) is now a realistic therapeutic target in every patient

with Rheumatoid Arthritis (RA). To assess it, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) proposed a Boolean definition of remission, which requires that tender joint count (TJC28), swollen joint count (SJC28), CReactive Protein (CRP, in mg/dl), and patient global assessment (PGA, 0-10 scale) are all ≤1. Although being stringent, this was elected as the preferred definition to use in daily care of RA.

PGA is the sole patient reported outcome (PRO) included in the currently accepted definitions of treatment target, namely in the definitions of remission endorsed by ACR/EULAR. The inclusion of PGA in the ACR/EULAR provisional definition of remission was justified because its responsiveness to effective treatment has been demonstrated in clinical trials. However, several studies have shown that PGA is not solely influenced by RA disease activity, but also influenced by sociodemographic features, geographic area, and cultural and ethnic aspects, reflecting the fact that PGA scores can be influenced by physical and psychological factors, comorbidities and fibromyalgia, among others.

Patients that fail only one of the four Boolean criteria have been called "near-remission" (designation applied when PGA is the solely criteria>1). Previous studies demonstrated that the proportion of near-remission patients could vary which can represent up to four times the proportion of patients in remission. Following current treatment guidelines this state of near-remission would justify intensification of immunosuppressive treatment. Immunosuppressive therapy, including biologic disease modifying anti-rheumatic drugs (bDMARDs), has been shown to improve PGA as disease activity evolves towards remission. However, in cases where PGA is being mainly driven by factors not related with RA, immunosuppressive therapy may not be able to lower PGA ≤1, despite SJC, TJC and CRP scores ≤1 having already been achieved. From this stage onwards, PGA is not dependent on disease activity and the inability to improve it further should not be interpreted as a failure of the immunosuppressive therapy.

These considerations led us into the proposal that the target for immunosuppressive therapy should be based on the concept of 3v-Remission: SJC, TJC, and CRP are all ≤1.This concept, however, can only be robustly established if we can demonstrate that ignoring the PGA in the target will not hinder the long-term efficacy of the intervention in terms of function and, especially structural damage. Please note that the authors do not question the crucial importance of incorporating PROs in the assessment of RA and the treatment decision process. They just question whether PGA is appropriate to guide immunosuppressive therapy, at least in LDA states.

Research objectives

- To assess whether two definitions of disease remission (including and excluding PGA) differ in their prediction of long-term radiographic damage in patients with RA.
- To assess whether two definitions of disease remission (including and excluding PGA) differ in their prediction of long-term physical function in patients with RA.

Requested study
DE013: A Prospective Multi-Centre Randomized, Double-Blind, Active Comparator-Controlled, Parallel-Groups Study Comparing the Fully Human Monoclonal Anti-TNFα Antibody Adalimumab Given Every Second Week With Methotrexate Given Weekly and the Combination of Adalimumab and Methotrexate Administered Over 2 Years in Patients With Early Rheumatoid Arthritis (PREMIER).

DE019: A Multi-Center Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab in Rheumatoid Arthritis Patients Currently Receiving Treatment With Methotrexate.

Funding source of research
None

Potential conflicts of interest
Act as a consultant for pharmaceutical company, participate in strategic advisory role for pharmaceutical company, principle/investigator on clinical studies and my organization receives funding/grant from pharmaceutical company.

Statistical analysis plan
Not available

Publication citation
This research request was transitioned to the Vivli.org data sharing platform. The final publication from this proposal will be posted on Vivli.org.

Proposal 2017-06

Title of the proposed research
RP1623 – Responsiveness of MRI Indices for Evaluation of Luminal Crohn's Disease Using a Central Image Management Solution.

Primary researcher(s)
Brian G. Feagan, M.D.

Affiliation
Robarts Clinical Trails, Inc.

Data sharing agreement date
16 May 2018

Research background/rationale
MRI is increasingly utilized in CD clinical trials. Over the last decade, there has been greater awareness of the importance of objective disease activity measurements (e.g., not basing on symptoms alone) in CD clinical trials. Requiring a baseline MRI at clinical trial entry could enable a non-invasive method for selecting a homogenous trial patient population, overcoming limitations of requiring endoscopy to include patients (e.g., ileal intubation). In addition, MRI may be more accurate than symptom-based measurement tools such as the Crohn's Disease Activity Index (CDAI) for the evaluation of the inflammatory status, and is also less invasive than endoscopy.

From a regulatory perspective, several conditions need to be met before MRI can be used as a valid instrument for assessment of inflammatory status in CD clinical trials.

First, the acquisition and quality of the MRI images should be standardized. For this purpose, Robarts Clinical Trials Inc. (Robarts) has developed a secure image acquisition, hosting and archiving system, referred to as Central Image Management Solutions (CIMS), to ensure adequate image quality and compliance to the privacy regulations. Since central adjudication has the potential to reduce error or variability in outcome evaluation, central adjudication by trained experts using standardized methodology is often a preferred method for outcome assessment, and is the core feature of the Robarts CIMS process. Adequate image quality and adherence to standardized MRI

protocol is first confirmed through a quality review process and compliance to the requirements of privacy regulations is ensured before distribution to central readers for assessment.

Second, a fully validated MRI index should be used to evaluate CD activity, with proven validity, reliability, and responsiveness, as introduced above. To date, the MaRIA and the London indices (London index and "extended" London index) have been formally derived and assessed in preliminary single-center validation studies. The MaRIA index was also part of a recent feasibility study, which included reliability assessments, but in a small sample of 20 subjects. Robarts recently completed a large reliability study of existing MRI indices for evaluation of CD.

The MaRIA index and London indices all showed "almost perfect" intra- rater reliability with Interclass Correlation Coefficients (ICCs) > 0.8, and all showed "substantial" inter-rater reliability based on point estimates between 0.6 and 0.8. However, the assessment of the rectum scored poorly, and in addition, some of the analyzed components still had suboptimal reproducibility. These results were evaluated during a subsequent Delphi process in order to identify possible reasons behind disagreement and suggested actions for improvement of the MaRIA scoring index. The Delphi consensus resulted in a series of statements/modifications which were then evaluated for consensus in an online survey after the meeting. This process resulted in the refinement/optimization of the MaRIA index for which we now also aim to assess responsiveness of its components items.

The CALM trial (M11-271) is a completed open-label study of 2 treatment algorithms that employ the use of prednisone, adalimumab, and azathioprine; all are treatments of known efficacy.

The primary endpoint of the trial was rate of mucosal healing as defined by a Crohn's Disease Endoscopic Index of Severity (CDEIS) score less than 4 and no deep ulcerations on ileocolonoscopy at 48 weeks after randomization. From the total patients in the trial, a subgroup of 37 patients from selected sites had paired MRI's available from before and after treatment. The aim of the current study is to assess the responsiveness of existing MRI indices for assessment of CD in a population of patients that have CD affecting the ileum, colon, or both and their component items (descriptors), using the CALM study dataset.

RATIONALE

There is need for a refined index for the assessment of CD activity (including small bowel activity) for use in clinical trials and to facilitate novel drug development. We aim to assess responsiveness of existing CD MRI indices (and their component descriptors).

Research objectives

The primary objective of this study is to:

- Determine the responsiveness of existing luminal MRI indices that measure CD disease severity (the optimized MaRIA, London and "extended" London) and their component items (descriptors) using:
    - Correlations among observed change scores in indices/descriptors compared to other clinical and/or endoscopic change scores (external responsiveness)
    - Standardized effect sizes and Guyatt's responsiveness statistic (internal responsiveness) based on the following criteria for change: a decrease of more than one half the standard deviation of the Visual Analogue Scale (VAS).

Exploratory objectives may include:

- Using items (descriptors) that were both reliable and responsive, to develop (or refine) a composite index for small bowel CD using the VAS as an anchor.

Requested study & MRI images
M11-271: An Open-Label, Multicenter, Efficacy and Safety Study to Evaluate Two Treatment Algorithms in Subjects with Moderate to Severe Crohn's Disease

Funding source of research
Robarts will cover the costs for writing and publication.

Potential conflicts of interest
Several: Consulting to Pharmaceutical (Pharma) company, Advisory board/steering committee member for Pharma company, Honorarium from Pharma company, Principle investigator & Investigator for clinical studies. Potential conflicts of interest will be assessed for authors at the time of manuscript development.

Statistical analysis plan
Not available.

Publication citation
The data request was withdrawn by the researcher after the data sharing agreement was signed. No study publication will be provided for this request.

Beyond scope of the PhRMA/EFPIA principles

Proposal 2014-02

Title of the proposed research
Impact of disease aetiology on response/overall survival in patients with advanced hepatocellular carcinoma receiving anti-angiogenic agents

Primary researcher
Philip J. Johnson, M.D.

Affiliation
University of Liverpool

Data sharing agreement date
02 Sep 2014

Research background/rationale
There have been several suggestions that overall survival in patients with advanced hepatocellular carcinoma receiving anti-angiogenic agents occurs primarily in patients where the aetiology is chronic hepatitis C virus infection. Conversely, where aetiology is related to hepatitis B or alcohol

abuse impact appears less. To-date numbers of patients available for analysis is too small to come to any firm conclusion—hence the present study.

Research objectives
Primary: To undertake a meta-analysis of relevant trials, so as to assess impact of aetiology on survival in patients with advanced hepatocellular carcinoma receiving anti-angiogenic agents.
Secondary: As above, but investigating tumour response rather than overall survival

Requested study
M10-963: An Open-label, Randomized Phase 3 Study of the Efficacy and Tolerability of Linifanib (ABT-869) Versus Sorafenib in Subjects With Advanced Hepatocellular Carcinoma (HCC)

Funding source of research
None

Potential conflicts of interest
Several: Advisory board committee member for a pharma company and lecturer for a pharma company.

Statistical analysis plan
The SAP report has been provided here.

Publication citation
Impact of Viral Status on Survival in Patients Receiving Sorafenib for Advanced Hepatocellular Cancer: A Meta-Analysis of Randomized Phase III Trials
Richard Jackson and Eftychia-Eirini Psarelli, Liverpool Cancer Trials Unit; Sarah Berhane and Philip Johnson, University of Liverpool, Liverpool; Harun Khan, Imperial College London, London; and Philip Johnson, The Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, United Kingdom.
DOI: 10.1200/JCO.2016.69.5197
PMID: 28045619

Proposal 2014-03

Title of the proposed research
Predictors of Carotid Intima-Media Thickness Progression in the FIRST Trial (NCT00616772).

Primary researcher
Kevin C. Maki, Ph.D.

Affiliation
Midwest Center for Metabolic & Cardiovascular Research, Glen Ellyn, IL

Data sharing agreement date
10 October 2014

Research background/rationale
The FIRST trial investigated the influence of fenofibric acid (FA), compared with placebo, on progression of carotid intima-media thickness (cIMT) in subjects with elevated triglycerides (TG; >=150 mg/dL) and below-average HDL cholesterol (HDL-C; <=45 mg/dL for men, <=55 mg/dL for women) during statin (atorvastatin) therapy. Overall, the results showed no significant effect of

treatment with fenofibric acid on the cIMT progression rate during the two-year treatment period. In some pre-specified subgroups (4 of 24) categorized by baseline characteristics, there was evidence of a reduced rate of cIMT progression in the FA group: (1) >60 years of age, (2) cIMT>0.795 mm, (3) TG 170-235 mg/dL, (4) history of coronary artery disease (Davidson et al. ATVB 2014;34:1298-1306). The primary aim of the proposed exploratory analyses is to investigate relationships between baseline, on-treatment levels, and changes from baseline in cardiometabolic risk factors and progression of cIMT. A secondary objective is to investigate relationships between measured cardiometabolic risk factors and changes in those risk factors. The proposed analyses will be helpful for hypothesis generation to assist with the design of future studies to investigate the impact of the high TG/low HDL-C phenotype on atherosclerotic disease risk and interventions intended to lower risk in such individuals.

Research objectives
Primary: To investigate cardiometabolic risk factors (baseline, on-treatment levels and changes from baseline) as predictors of cIMT progression in both treatment groups and possible treatment by risk factor interactions.
Secondary: To investigate relationships among individual cardiometabolic risk factors and changes from baseline in those risk factors.

Requested study
M10-158: Evaluation of Choline Fenofibrate (ABT-335) on Carotid Intima-Media Thickness (cIMT) in Subjects With Type IIb Dyslipidemia With Residual Risk in Addition to Atorvastatin Therapy (FIRST) Trial.

Funding source of research
None

Potential conflicts of interest
Several: Consulting to pharmaceutical (pharma) companies, advisory board/steering committee member for pharma companies and my organization receives research funding from a pharma company.

Statistical analysis plan
The proposed analyses will focus on predictors of cIMT progression within treatment groups, with tests for heterogeneity of effect to investigate possible treatment group by cardiometabolic risk factor interactions. This approach is analagous to that taken by Albers et al. in their analysis of predictors of cardiovascular events in the AIM-HIGH trial (Albers et al. JACC 2013;62:1575-1579.) However, instead of using Cox proportional hazards modeling of time to first event, the dependent variable of primary interest in AIM-HIGH, the proposed investigation will use multivariate linear regression to analyze results for progression rate as a continuous variable and multivariate logistic regression to model progression as a dichotomous variable (0 = no, 1 = yes).

Because prior work by our group has shown that baseline cIMT is a strong predictor of cIMT progression rate (Maki et al. Journal of Clinical Lipidology 2011;5, 141–151, Maki et al. Vascular Health and Risk Management 2012;8 31–38), and because the treatment groups differed in baseline cIMT (Davidson et al. ATVB 2014;34:1298-1306), the baseline cIMT value will be included in all models as a covariate. In order to maximize statistical power, cardiometabolic risk factors will generally be used as continuous variables, although natural log or rank transformations may be employed for variables that show substantial departures from normal distributions. Last observation carry-forward will be used to account for missing data points. For individual cardiometabolic risk factor variables, models will be included with adjustment for baseline cIMT only; baseline cIMT plus age, sex, central imaging site, and atorvastatin dose; and a fully adjusted model that includes other

variables that were significant predictors in baseline cIMT adjusted models. This is similar to what the investigators have done for other analyses of predictors of cIMT progression (Maki et al. Journal of Clinical Lipidology 2011;5, 141–151, Maki et al. Vascular Health and Risk Management 2012:8 31–38). Quadratic functions and analyses based on quantile (e.g., tertile) categories may also be assessed to investigate the nature of some associations if scatterplots suggest non-linear relationships.

For secondary analyses to assess relationships between cardiometabolic risk factors and changes in cardiometabolic risk factors, univariate and multivariate linear regression analyses will be employed.

For all relevant variables, descriptive statistics will be generated including mean and standard deviation or median and interquartile range limits for continuous variables and frequencies and percentages for nominal variables. No adjustments will be employed for multiple comparisons and two-sided p-values < 0.05 will be considered statistically significant.

No formal sample size and power calculations were completed because the analyses proposed are exploratory and based on a pre-existing data set.None of the analyses completed and published in the manuscript reporting the main study results (Davidson et al. ATVB 2014; 34:1298- 1306) will be repeated for the proposed analyses.

Publication citation
Discordance of Low-Density Lipoprotein Cholesterol With Alternate Lipid Measures in Statin-Treated Men and Women With Mixed Dyslipidemia
Kevin Maki, Ph.D., Mary Dicklin, Ph.D., Margie Bell, B.S., Michael Davidson, M.D.
DOI: https://doi.org/10.1016/j.jacl.2017.04.007

Proposal 2014-04

Title of the proposed research
Fibrates for primary prevention of cardiovascular disease events.

Primary researcher
Alain Nordmann, M.D.

Affiliation
Institute for Clinical Epidemiology & Biostatistics, University Hospital Basel, Switzerland

Data sharing agreement date
06 January 2015

Research background/rationale
In this systematic review and meta-analysis we will evaluate the effects of fibrates vs. placebo or usual care, or fibrates plus other lipid modifying drugs versus other lipid-modifying drugs alone or fibrates versus placebo or usual care on patient-relevant clinical outcomes. Currently available fibrates in North America and/or Europe include: gemfibrozil, fenofibrate, fenofibric acid, bezafibrate, and ciprofibrate. Recent investigations indicate that the effects of fibrates are mediated, at least in part, through alterations in transcription of genes encoding for proteins that control lipoprotein metabolism. Fibrates activate specific transcription factors belonging to the nuclear hormone receptor superfamily, termed peroxisome proliferator-activated receptors (PPARs). The PPAR- form mediates fibrate action on HDL-C levels via transcriptional induction of synthesis of the major HDL

apolipoproteins, apoA-I and apoA-II. Fibrates lower hepatic apoC-III production and increase lipoprotein lipase-mediated lipolysis via PPAR.
Fibrates stimulate cellular fatty acid uptake, conversion to acyl-CoA derivatives, and catabolism by the ß-oxidation pathways, which, combined with a reduction in fatty acid and triglyceride synthesis, results in a decrease in VLDL production. In summary, both enhanced catabolism of triglyceride-rich particles and reduced secretion of VLDL underlie the hypotriglyceridemic effect of fibrates, whereas their effect on the HDL metabolism is associated with changes in HDL apolipoprotein expression. Potential side or adverse effects from fibrate therapy are increased venous thrombotic events, pancreatitis, reversible rise in creatinine (described with all fibrates except gemfibrozil), rise in homocysteine, and elevations in transaminases and myositis/rhabdomyolysis in particular for combinations of gemfibrozil with statins.

Research objectives
Primary: To assess the clinical benefit and harm of fibrates versus placebo or usual care or fibrates plus other lipid-modifying drugs versus other lipid-modifying drugs alone for the primary prevention of CVD events and mortality.

Requested study
M10-158: Evaluation of Choline Fenofibrate (ABT-335) on Carotid Intima-Media Thickness (cIMT) in Subjects With Type IIb Dyslipidemia With Residual Risk in Addition to Atorvastatin Therapy (FIRST) Trial

Funding source of research
The Basel Institute for Clinical Epidemiology and Biostatistics is supported by grants from Santésuisse and from the Gottfried and Julia Bangerter-Rhyner-Foundation.

Potential conflicts of interest
None

Statistical analysis plan
The SAP report has been provided here.

Publication citation
Fibrates for primary prevention of cardiovascular disease events.
Jakob T, Nordmann AJ, Schandelmaier S, Ferreira-González I, Briel M. Art. No.: CD009753.
DOI: 10.1002 /14651858.CD009753.pub2.

Proposal 2015-04

Title of the proposed research
Individual progression of carotid intima media thickness as a surrogate for vascular risk (PROG-IMT)

Primary researcher
Matthias W. Lorenz, M.D.

Affiliation
Frankfurt University Hospital, Germany

Data sharing agreement date
15 October 2015

Statistical analysis plan
Not available.

Publication citation
The data request was withdrawn by the researcher after the data sharing agreement was signed. No study publication will be provided for this request.

Proposal 2015-05

Title of the proposed research
Impact of disease aetiology on response/overall survival in patients with advanced hepatocellular carcinoma receiving anti-angiogenic agents

Primary researcher
Philip J. Johnson, M.D.

Affiliation
University of Liverpool

Data sharing agreement date
22 Sep 2015

Research background/rationale
There have been several suggestions that overall survival in patients with advanced hepatocellular carcinoma receiving anti-angiogenic agents occurs primarily in patients where the aetiology is chronic hepatitis C virus infection. Conversely, where aetiology is related to hepatitis B or alcohol abuse impact appears less. To-date numbers of patients available for analysis is too small to come to any firm conclusion hence the present study.

Research objectives
Primary: To undertake a meta-analysis of relevant trials, so as to assess impact of aetiology on survival in patients with advanced hepatocellular carcinoma receiving anti-angiogenic agents.
Secondary: As above, but investigating tumor response rather than overall survival, and assessing the impact of liver function on measures of survival as defined by a recently developed model "ALBI".

Requested study
M10-963: An Open-label, Randomized Phase 3 Study of the Efficacy and Tolerability of Linifanib (ABT-869) Versus Sorafenib in Subjects With Advanced Hepatocellular Carcinoma (HCC)

Funding source of research
None

Potential conflicts of interest
Several: Advisory board committee member for a pharma company and lecturer for a pharma company.

Statistical analysis plan
The SAP report has been provided here.

Publication citation
DOI: 10.1200/JCO.2016.69.5197

Proposal 2016-05

Title of the proposed research
Impact of disease aetiology on response/overall survival in patients with advanced hepatocellular carcinoma receiving anti-angiogenic agents

Primary researcher
Philip J. Johnson, M.D.

Affiliation
University of Liverpool, United Kingdom

Data sharing agreement date
2 June 2017

Research background/rationale
In a previous collaboration with Abbvie, it was demonstrated that aetiology has a significant impact on response of HCC to sorafenib using the M10-963 study. With information from this collaboration a new, and extensively validated, model to assess liver function in patients with HCC- the 'ALBI score" was developed.

The next step is to examine how liver function (as assessed by the ALBI score) deteriorates during the course of targeted therapies in patients with advanced HCC. This only requires serial values for serum albumin and bilirubin but other study parameters have also been requested for comparison with the more conventional ways of assessing liver function.

Research objectives
Primary: To document the changes in liver function (in Aggregate) according to aetiology.
Secondary: To document the changes in fibrosis as assessed by the derived function FIB-4 index, and the platelet count.

Requested study
M10-963: An Open-label, Randomized Phase 3 Study of the Efficacy and Tolerability of Linifanib (ABT-869) Versus Sorafenib in Subjects With Advanced Hepatocellular Carcinoma (HCC)

Funding source of research
None

Potential conflicts of interest
Act as an advisory board committee member and lecturer for a pharma company.

Statistical analysis plan
The SAP report has been provided here.

Publication citation
DOI: 10.1016/j.jhep.2021.05.015.

Proposal 2016-06

Title of the proposed research
Evaluating the Placebo Endoscopic Response in Crohn's Disease Clinical Trials

Primary researcher
Vipul Jairath, M.D., Ph.D.

Affiliation
Robarts Clinical Trials, Inc., Canada

Data sharing agreement date
16 May 2017

Research background/rationale
Due to evolving trial design, the use of endoscopic mucosal healing as an endpoint requires an understanding of the evolution of endoscopic activity in trial subjects receiving placebo. Data from subjects randomized to placebo will be used to help in development/design of randomized trials, particularly in calculating samples sizes.

Research objectives
Primary: Describe the evolution of endoscopic mucosal healing through change in the endoscopic scores (Simplified Endoscopy Score for CD [SES_CD], Crohn's Disease Endoscopic Index of Severity [CDEIS] in patients with CD who participated in clinical trial and were randomized to placebo treatment.
Secondary: Provide a pooled estimate of the endoscopic placebo response rate in CD trials. Identify factors associated with spontaneous improvement in endoscopic mucosal healing in patients with CD who participated in a clinical trial and were randomized to placebo treatment.

Requested study
M15-993/BI 655066/ABBV-066 (Risankizumab) : A Phase II, Randomized, Double-Blind, Active-Controlled Study to Assess the Safety and Efficacy of NBI-56418 in Subjects with Endometriosis

Funding source of research
None

Potential conflicts of interest
Consultant, advisory board member and earned an honorarium from a pharma company. Principle/investigator for clinical trials and organization receives funding/grants from pharma companies.

Statistical analysis plan
The SAP report has been provided here.

Publication citation
DOI: https://doi.org/10.1016/j.cgh.2019.08.025

Proposal 2017-04

Title of the proposed research
Comparative safety and effectiveness of cognitive enhancers for Alzheimer's dementia: a systematic review and individual patient data network meta-analysis

Primary researcher
Sharon Straus, M.D. & Andrea Tricco, Ph.D.

Affiliation
St. Michael's Hospital, Toronto, Canada

Data sharing agreement date
17 October 2017

Research background/rationale
Alzheimer's dementia (AD) is the most common cause of dementia and has an insidious onset with progressive deterioration in cognition (eg, memory, thinking and perception), function, behaviour and mood. To date, 46.8 million people worldwide live with dementia. This number will almost double every 20 years, and it is estimated to reach 131.5 million by 2050. A study showed that as age increases, the rates of AD increase overall for both men and women, but it is more prevalent in women (rate/100 years=2.50 (1.85–3.41)) than men (rate/100 years=1.89 (1.22–2.94)). It is currently unclear if galantamine, rivastigmine or donepezil should be used by patients with severe AD, and whether memantine is the most optimal treatment for severe AD. The use of acetylcholinesterase inhibitors and increased doses of donepezil in patients with dementia increase the risk of bradycardia, as well, cholinesterase inhibitors double the risk of hospitalization for bradycardia in older patients. Also, the use of other medications may increase risk of adverse events. For example, cardiac medications like β-blockers may increase risk of bradycardia, and anti-inflammatories may increase risk for gastrointestinal upset.

A systematic review and network meta-analysis (NMA) of aggregated data was previously attempted but was unable to provide definitive conclusions regarding the influence of patient characteristics on the results. In this study, the results are tailored to age, AD severity, comorbidity, and study duration via subgroup analysis. The use of individual patient data (IPD) will increase power and will help explain the relationship between treatment effects and patient-level characteristics.

Research objectives
Primary: The aim of this study is to examine the comparative effectiveness and safety of cognitive enhancers versus placebo or best supportive care by patient characteristics, such as AD severity and sex. The IPD-NMA data will be used to identify potential treatment effect modifiers and estimate the most effective and safest treatments for patients with different characteristics. The outputs of the project are to provide clinicians, patients and caregivers with tailored evidence to inform their decision making, improving the health of patients living with AD.

Requested study
M10-822: A randomized study of H3 antagonist ABT-288 in mild-to-moderate Alzheimer's dementia

M10-984: A phase 2 randomized, controlled trial of the α7 agonist ABT-126 in mild-to-moderate Alzheimer's dementia

Funding source of research

- ACT is funded by a Tier 2 Canada Research Chair in Knowledge Synthesis.
- AAV is funded by the Canadian Institutes of Health Research (CIHR) Banting Postdoctoral Fellowship Program.
- SES is funded by a Tier 1 Canada Research Chair in Knowledge Translation.
- This research is funded by the CIHR Drug Safety and Effectiveness Network (grant number 137713).

Potential conflicts of interest
Investigator for clinical trials

Statistical analysis plan
Not available

Publication citation
This research request was transitioned to the Vivli.org data sharing platform. The final publication from this proposal will be posted on Vivli.org.