

**The YODA Project  
Research Proposal Review**

The following page contains the final YODA Project review  
approving this proposal.

**The YODA Project**  
**Research Proposal Review - Final**  
**(Protocol #: 2018-3743 )**

**Reviewers:**

- Nihar Desai
- Cary Gross
- Harlan Krumholz
- Richard Lehman
- Joseph Ross

**Review Questions:**

**Decision:**

- |   |                            |
|---|----------------------------|
| 1. Is the scientific purpose of the research proposal clearly described?  | Yes                        |
| 2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health? | Yes                        |
| 3. Can the proposed research be reasonably addressed using the requested data?  | Yes, or it's highly likely |
| 4. Recommendation for this data request:  | Approve                    |

**Comments:**

No additional comments.

**The YODA Project  
Research Proposal Review**

Revisions were requested during review of this proposal.  
The following pages contain the original YODA Project review and  
the original submitted proposal.

**The YODA Project**  
**Research Proposal Review - Revisions Requested**  
**(Protocol #: 2018-3743 )**

**Reviewers:**

- Nihar Desai
- Cary Gross
- Harlan Krumholz
- Richard Lehman
- Joseph Ross

**Review Questions:**

**Decision:**

- |   |                            |
|---|----------------------------|
| 1. Is the scientific purpose of the research proposal clearly described?  | No                         |
| 2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health? | Yes                        |
| 3. Can the proposed research be reasonably addressed using the requested data?  | Yes, or it's highly likely |
| 4. Recommendation for this data request:  | Not Approve                |

**Comments:**

This is a well conceived proposal to use data available via the YODA Project to examine changes in HRQoL in the context of receiving biologic treatment among patients with Crohn's disease. However, certain aspects of the study should be clarified prior to approval. The outcome variable is clear (changes in HRQoL), but the statistical analysis plan offers explanation for analyses dependent upon whether the outcome is continuous or categorical - isn't the outcome a continuous variable. Also, there are instances in the proposal where examination of adverse events (harm) is discussed - but these outcomes are not defined. Finally, the investigators explain that no other variables of interest will be used or examined. But that seems unlikely. Will subgroup analyses by patient age, sex, disease severity, etc. not be pursued? Would suggest clarifying these points prior to approving the proposal.

## Principal Investigator

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**State or Province:** Rijeka  
**Zip or Postal Code:** 51000  
**Country:** Croatia

## General Information

### Key Personnel (in addition to PI):

**First Name:** Mirjana  
**Last name:** Stanic Benic  
**Degree:** MD  
**Primary Affiliation:** UHC Rijeka  
**SCOPUS ID:** 57147840000

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

**How did you learn about the YODA Project?:** Internet Search

## Conflict of Interest

[http://yoda.yale.edu/system/files/yoda\\_project\\_coi\\_form\\_for\\_data\\_requestors\\_2018\\_0.pdf](http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2018_0.pdf)

## Certification

**Certification:** All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

**Data Use Agreement Training:** As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

### Associated Trial(s):

1. [NCT00207766 - ACCENT II - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNF Chimeric Monoclonal Antibody \(Infliximab, Remicade\) in the Long Term Treatment of Patients With Fistulizing CROHN'S Disease](#)
2. [NCT00771667 - A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Ustekinumab Therapy in Subjects With Moderately to Severely Active Crohn's Disease Previously Treated With T](#)
3. [NCT01369329 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Have Failed](#)
4. [NCT01369342 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease \(UNITI-2\)](#)

[5. NCT01369355 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease](#)

**What type of data are you looking for?:** Full CSR

## Research Proposal

### Project Title

The impact of biological interventions on health-related quality of life in adults with Crohn's disease

### Narrative Summary:

Crohn disease is a very aggressive inflammatory gastrointestinal disease which substantially decrease health-related quality of life in patients. Different strategies are involved to influence on disease course (surgery, drug treatment). Biologic drugs represent a revolution in this field of medicine decreasing disease symptoms. The aim of this study is to examine if biologicals could influence on health-related quality of life which represent a final goal for the patients.

### Scientific Abstract:

**Background:** Recent studies often reported QoL outcomes in addition to clinical disease activity indices of biological treatment in patients with Crohn's disease. However, no systematic review has examined QoL outcomes in these specific patients populations treated with biologic agents.

**Objective:** To systematically assess the beneficial and harmful effects of the biologic treatment on HRQoL outcomes in people with Crohn's disease.

**Study Design:** Cochrane Systematic review with meta-analysis.

**Participants:** Adults (>18 years of age) with Crohn's disease as defined by a combination of clinical, biochemical, radiological, endoscopic and histological criteria and treated with biological drugs will be considered for the inclusion.

**Main Outcome Measure:** Change in HRQoL scores as defined by the included studies.

**Statistical Analysis:** For continuous outcomes, we will calculate the mean difference (MD) and corresponding 95% confidence interval (95% CI) if the same tool has been used to measure the same outcome across different studies. We will calculate the standardized mean difference (SMD) when different tools have been used to measure the same underlying construct. For dichotomous outcomes, we will calculate the risk ratio (RR) and corresponding 95% CI.

### Brief Project Background and Statement of Project Significance:

HRQoL represents a functional effect of the disease and it is one of the main issues in people with CD. Modifying the disease course, the biological treatment may have a substantial effect on HRQoL and therefore would be beneficial to be introduced earlier in the treatment with regard to HRQoL outcomes (Bodger 2002). Studies increasingly include HRQoL as a secondary outcome and no systematic review has clearly established the evidence for an improvement in HRQoL in this population. A previous literature review on the impact of biologics on HRQoL in IBD patients has been limited in the scope and time of the articles retrieved (IBD population, including both CD and ulcerative colitis) and methodological concept (articles only in English, only IBDQ and SF-36 as outcome measures) (Vogelaar 2009). This review endeavors to address an up-to-date critical view of growing evidence on the impact of biological interventions in improving HRQoL in people with CD.

### Specific Aims of the Project:

The aim of this project is to systematically assess the beneficial and harmful effects of the biologic treatment on HRQoL outcomes in people with

Crohn's disease. The main hypothesis is that biological drugs could have a positive impact on health-related quality of life.

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

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations  
Summary-level data meta-analysis  
Summary-level data meta-analysis pooling data from YODA Project with other additional data sources  
Research on comparison group

## Research Methods

**Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:**

The following databases will be searched: MEDLINE (via PubMed; 1946 to present); Embase (via Ovid; 1974 to present); the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library current issue); the Cochrane IBD Inflammatory Bowel Disease and Functional Bowel Disorders Specialized Trial Register (IBD/FBD Group Specialized Register), Science Citation Index Expanded (SCIE) ( Institute for Scientific Information Web of Knowledge), Digestive Disease Week (DDW) abstracts of RCTs (1981 to present. Inclusion criteria are: RCTs assessing the impact of biological interventions on HRQoL in people with Crohn's disease irrespective of publication status, language, or blinding procedure will be included. Studies assessing all recognized biological interventions for the treatment of Crohn's disease will be considered for evaluation (e.g. infliximab, adalimumab, certolizumab pegol, natalizumab, ustekinumab, briakinumab, vedolizumab, and recombinant human interleukin 10). The comparison will be a placebo or an active comparator. Exclusion criteria: no diagnosis of Crohn, no treatment with biologicals and no HRQL results.

**Main Outcome Measure and how it will be categorized/defined for your study:**

Primary outcomes

1. Change in HRQoL scores as defined by the included studies.

From requested studies within Yoda, we will extract data on HRQL results (mainly IBDQ results) as a baseline and final means +/- S.D. OR medians + interquartile range for all groups of patients investigated. So, we urgently need data for the whole groups, not patient-level individual data. For example, if there are two groups of patients, one treated with adalimumab and another with placebo, we need these data: baseline and final IBDQ scores for the placebo group and baseline and final IBDQ scores for the adalimumab-treated group.

**Main Predictor/Independent Variable and how it will be categorized/defined for your study:**

Therapeutic option (biological drug, placebo) will be an independent variable which will define groups of patients for analysis.

**Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:**

There is no other variable of interest, except the above stated - main outcome (Change in HRQoL scores as defined by the included studies: means +/- S.D. OR medians + Interquartile range.)

**Statistical Analysis Plan:**

Measures of treatment effect

For continuous outcomes, we will calculate the mean difference (MD) and corresponding 95% confidence interval (95% CI) if the same tool has been used to measure the same outcome across different studies. We will calculate the

standardized mean difference (SMD) when different tools have been used to measure the same underlying construct.

For dichotomous outcomes, we will calculate the risk ratio (RR) and corresponding 95% CI. Where studies report adverse events as dichotomous data, we will report on the proportion of participants experiencing the event in each study arm. We will report descriptive results for adverse event data that cannot be extracted as dichotomous outcomes as described above (Higgins 2011).

Unit of analysis issues

If there are multiple observations for the same outcome, we will make an effort to combine outcomes for fixed

#### follow-up

intervals. We plan to evaluate outcomes at maximum follow-up as defined by individual studies. For cross-over trials, we will use data from the first phase of the trial (i.e. before any cross-over). HRQoL outcomes and safety among different doses of biological drugs will be compared using subgroup analyses where possible. Studies with control groups using different types of interventions (e.g. placebo or active treatment), studies with cluster randomised treatment groups and studies with multiple treatment groups e.g. dose groups) will be analysed separately and will not be combined in a single meta-analysis.

#### Dealing with missing data

We will attempt to contact the authors of included studies to obtain missing data. In the case of missing data despite our attempts to contact authors, the following strategies will be considered. For missing dichotomous outcomes, two scenarios will be considered, the best-case scenario in which all patients with incomplete data will be assumed to be a treatment success with regard to QoL and a worst-case scenario in which all patients with incomplete data will be assumed to be treatment failures with regard to QoL. We will use sensitivity analysis to assess the impact of these assumptions on the effect estimate. We will use an available case analysis for missing continuous outcomes and assumptions about participants with missing data will not be made. We will contact the authors of studies published in abstract form for relevant missing data and these studies will only be included in the review if enough data are provided to assess outcomes and risk of bias.

#### **Project Timeline:**

All analysis should be finished to the end of January 2019. To the end of February 2019 systematic review should be published.


#### **Dissemination Plan:**

the Cochrane review will be available through the Cochrane platform online and published in the Cochrane Database of Systematic Reviews.

#### **Bibliography:**

Stanic Benic M, Giljaca V, Vlahovic Palcevski V. The impact of biological interventions on health-related quality of life in adults with Crohn's disease. Cochrane Database of Systematic Reviews 2018, Issue 2. Art. No.: CD012973. DOI: 10.1002/14651858.CD012973. Available online at <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012973/full>

#### **Supplementary Material:**

 [msb\\_the\\_impact\\_of\\_biological\\_interventions\\_on\\_health-related\\_quality\\_of\\_life\\_in\\_adults\\_with\\_crohns\\_disease\\_copy-edited\\_21\\_feb\\_2018.pdf](#)