The YODA Project
Research Proposal Review

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

The Yale University Open Data Access (YODA) Project
Yale University Center for Outcomes Research and Evaluation (CORE)
1 Church Street, Suite 200, New Haven, CT 06510

The YODA Project
Research Proposal Review - Final
(Protocol #: 2021-4683)

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:

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 Yale University Open Data Access (YODA) Project
Yale University Center for Outcomes Research and Evaluation (CORE)
1 Church Street, Suite 200, New Haven, CT 06510

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2021-4683)

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?	Unsure, would defer to Data Holder Due Diligence Assessmen
4. Recommendation for this data request:	Not Approve

Comments:

1. This is a very ambitious scoping project looking for associations between antiinfective drug prescribing and measures of progression or amelioration across a range of neurological conditions. The requestors have asked for datasets from a range of trials. The validity of their findings will depend critically on the availability of detailed prescribing information and on the use of statistical analysis which can cope with great heterogeneity in outcome measures. Anti-infective drugs are usually prescribed over short periods of time varying from a single dose to a week or two; the researchers need to clarify what they will do if this information is not consistently available in all the trials requested.

2. These studies are short-term in BPSD with no long-term follow up of the progression of the underlying disease. Please clarify why the studies were selected. Changes in the MMSE will be artifactual.

3. Specific to the Risperdal studies, antibacterial use is documented in all three short term studies. RIS-AUS-5 has high usage, RIS-USA-232 and RIS-USA-63 have average to low usage for this population. Data are collected at each visit. It is unclear how well it was documented in terms of dose and duration. The MMSE measures cognitive decline and AD usually progresses at 2-3 points per year. It was measured at visit 1 and last visit or study end for RIS-AUS-5 and RIS-USA-63. Considering that the patients who entered the study were severely agitated and the interval of < 1 year between scoring there will be no useful information on disease progression.

4. ELN115727-301 lists 916 uniquely annotated medications/vitamins/supplements/OTC and ELN115727-302 lists 832 but how many of these would be considered anti-infective and if every instance of short term use was recorded and the exact time frame of use would not be possible to determine.

5. It would be problematic to be certain about outcomes since the proposed analysis is well outside the scope of the trial and may lack consistency within the trial and certainly consistency with other trials would not have even been considered. Please clarify how you will address.

Principal Investigator

First Name: Chaim
Last Name: Singal
Degree: M.Sc In Mathematics & Statistics
Primary Affiliation: experimind ltd (Data Science and Sattsistics)
E-mail: chaim.singal@gmail.com
Phone number: 972-543348699
Address: Derech Namir 134 Flat 14 Tel Aviv , Israel
N/A
City: N/A
State or Province: Israel
Zip or Postal Code: 625054
Country: Israel

General Information

Key Personnel (in addition to PI):
First Name: Yossi
Last name: Gilgun-Sherki
Degree: PhD in Neurosciences; MBA in Health Innovation
Primary Affiliation: Primary Affiliation: None , Former Affiliation: Department of Neurology and the Felsenstein Medical Research Center, The Sackler School of Medicine, Tel Aviv University, Israel.
SCOPUS ID: NA

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?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_yossi_gilgun-sherki_0.pdf
https://yoda.yale.edu/system/files/yoda_coi_conflict_of_intrest_chaim_singal.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

1. NCT00236561 - TOPMAT-MIGR-003 - A Randomized, Double-Blind, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of Two Doses of Topiramate Compared to Placebo and Propranolol in the Prophylaxis of Migraine
2. NCT00210912 - CAPSS-276 - A Comparison of the Efficacy and Safety of Topiramate Versus Placebo for the Prophylaxis of Chronic Migraine
3. NCT00249158 - RIS-AUS-5/CR006010 - Risperidone in the Treatment of Behavioural and Psychological Signs and Symptoms in Dementia (BPSSD): a Multicentre, Double-blind, Placebo-controlled Parallel-group Trial
4. NCT00034762 - RIS-USA-232/CR002764 - Efficacy And Safety Of A Flexible Dose Of Risperidone Versus Placebo In The Treatment Of Psychosis Of Alzheimer's Disease

5. NCT00253123 - RIS-USA-63/CR006022 - A Randomized, Double-Blind, Placebo-Controlled Study of Risperidone for Treatment of Behavioral Disturbances in Subjects With Dementia
6. NCT00253214 - GAL-INT-10 - Placebo-Controlled Evaluation of Galantamine in the Treatment of Alzheimer's Disease: Safety and Efficacy of a Controlled-Release Formulation
7. NCT00236574 - CR003145 // GAL-INT-11 - A Randomized Double Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Galantamine in Patients With Mild Cognitive Impairment (MCI) Clinically at Risk for Development of Clinically Probable Alzheimer's Disease
8. NCT00236431 - GAL-INT-18 - A Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Galantamine in Patients With Mild Cognitive Impairment (MCI) Clinically at Risk for Development of Clinically Probable Alzheimer's Disease
9. NCT00679627 - GALALZ3005 - A Randomized, Double-Blind, Placebo-controlled Trial of Long-term (2-year) Treatment of Galantamine in Mild to Moderately-Severe Alzheimer's Disease
10. NCT00216619 - TOPMAT-MIG-303 - A Double-Blind, Randomized, Placebo-Controlled, Multicenter Trial to Investigate the Efficacy and Tolerability of Topiramate in Prolonged Migraine Prevention
11. GAL-USA-10 - Placebo-controlled evaluation of galantamine in the treatment of Alzheimer’s disease: Evaluation of safety and efficacy under a slow titration regimen
12. NCT00575055 - ELN115727-302 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Trial of Bapineuzumab (AAB-001, ELN115727) In Patients With Mild to Moderate Alzheimer's Disease Who Are Apolipoprotein E4 Carriers
13. NCT00574132 - ELN115727-301 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Trial of Bapineuzumab (AAB-001, ELN115727) In Patients With Mild to Moderate Alzheimer's Disease Who Are Apolipoprotein E4 Non- Carriers

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

The effects of systemic anti-infective concomitant medications on progression of neurological diseases

Narrative Summary:

Various evidence suggests neurological conditions may be induced or exacerbated by microbial infections. Furthermore, it has been shown that anti-infective medications may have neuroprotective properties. A retrospective cohort study was chosen for this research as this will enable us to examine many type of diseases, and many groups of medications, without the need to expose new patients for a new investigation by using existing data. The availability of clinical data from various randomized studies makes such data an attractive source for systematic research on many diseases and many groups of anti-infective medications. We will examine the effect of anti-infective agents on progression

Scientific Abstract:

BACKGROUND: One theory for the cause of neurological conditions is infection by pathological agents, including viruses, bacteria and fungi. These infections, and/or their treatment, may lead to dysbiosis and microflora imbalances in the gut. Anti-infective medications have demonstrated neuroprotective defense against various microorganisms.
OBJECTIVE: In this retrospective cohort study, we will aim to determine whether administration of systemic anti-infective medications has any impact on the progression of neurological diseases. We will also examine whether certain groups of these medications are more effective in altering neurological disease progression than others. We hypothesize that anti-infective medications may offer a therapeutic value for treating various neurological diseases, and other diseases with neurological manifestations. The study objectives will be to gather substantial data to support the hypothesis.
STUDY DESIGN: The proposed study design allows aggregation of a large datasets, examining multiple neurological diseases and anti-infective medications, without the need to perform expensive and time-consuming

clinical trials for each of the variables alone.
PARTICIPANTS: Participants from the placebo group in neurological clinical trials who were administered anti-infective drugs for reasons unrelated to the clinical trial will be assessed for changes in their neurological condition and compared with placebo patients not given anti-infectives.
MAIN OUTCOME MEASURE: This exploratory study will initially focus on each neurological condition (e.g., Parkinson's disease, etc.) and for each outcome (e.g., Unified Parkinson's Disease Rating Scale-UPDRS, etc.). If promising results are identified, we will try to combine data from multiple studies for the same disease with the same output measure and similar duration, to get a more comprehensive understanding of the relationship between the neurological pathology and treatment mechanisms with anti-infective agents.
STATISTICAL ANALYSIS: This will be a retrospective meta-analysis using chi-squared statistics to compare neurological disease progression between placebo group patients treated with anti infectives versus those that were not.

Brief Project Background and Statement of Project Significance:

Neurological pathologies, for example neurodegenerative diseases such as PD, AD and other dementias, or painful chronic conditions such as migraines, have been described by the World Health Organization (WHO) as one of the greatest public health challenges (5), requiring ongoing intervention. Therefore, research into identifying potential causes of these diseases is essential.
One theory for the cause of neurological conditions is infection by pathological agents, including viruses, bacteria and fungi (6, 7, 8, 9). Furthermore these infections, and/or the treatment for them, may lead to dysbiosis and microflora imbalances in the gut, which has been associated with various pathologies including neurological conditions (10, 11, 12, 13). In addition, anti-infective medications have demonstrated to provide neuroprotective defense against various microorganisms (14, 15, 16).
To further examine potential benefits of anti-infective medications as potential therapeutics for neurological pathologies, we are proposing to perform the current study, where we will examine the relationship between use of anti-infective agents and progression of neurological disease in placebo patients treated with anti-infective agents. The study will utilize data available from the YODA database, as well as several other similar databases, to review, and assess the potential efficacy of anti-infective medications, provided as a backup concomitant medications, in placebo patients participating in neurological clinical studies.
This will be a retrospective meta-analysis using chi-squared statistics to compare neurological disease progression between placebo group patients treated with anti-infectives versus those that were not. The study will focus on the following diseases, including PD, AD, Frontotemporal Dementia (FTD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), Migraine, Fibromyalgia and Systemic Lupus Erythematosus (SLE) in this project and future projects may be expanded to other neurological conditions. The knowledge obtained from this study will provide further data regarding the possible infection mechanisms involved in the pathogenesis of neurological disease, and whether anti-infective therapy may affect subsequent neurological disease processes. As a result these findings may offer potential avenues for diagnosing and treating neurological conditions, and positively modify their evolution. It is anticipated that the finding from this study may provide valuable insights that will justify further future clinical trials, in which the influence of identified mechanisms on disease progression would be examined.
The availability of clinical data from various randomized studies makes such data an attractive source for a systematic research, meta-analysis and data mining. These research methods offer valuable opportunities to examine diseases from different aspects than planned in the clinical trial design and identify novel features of disease pathology and treatment. Moreover, combining data from multiple clinical studies targeting the same population increases the statistical power of the analysis making the data more convincing and robust.

Specific Aims of the Project:

In this study, we will aim to determine whether administration of systemic anti-infective medications has any impact on the progression of neurological diseases. We will also examine whether certain groups of these medications are more effective in altering neurological disease progression than others.
We hypothesize that anti-infective medications may offer a therapeutic value for treating various neurological disease, and other diseases with neurological manifestations. The study objectives will be to gather substantial data to support the hypothesis.
The proposed study design allows aggregation of a large datasets, examining multiple neurological diseases and anti-infective medications, without the need to perform expensive and time-consuming clinical trials for each of the variables alone. Should interesting results be identified, i.e., evidence indicating an anti-infective medication may have an effect on neurological symptom progression, future clinical trials examining the effect directly may be conducted.

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

This exploratory study will initially focus on each neurological condition (e.g., PD, etc.) and for each outcome (e.g., Unified Parkinson's Disease Rating Scale-UPDRS, etc.).

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 using only data from YODA Project
Participant-level data meta-analysis
Participant-level data meta-analysis pooling data from YODA Project with other additional data sources

Research Methods

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

This study will utilize data available from the YODA & VIVLI database to assess the potential efficacy of anti-infective medications, provided as a backup concomitant medications, in placebo patients participating in neurological clinical studies.
This will be a retrospective meta-analysis using chi-squared statistics to compare neurological disease progression between placebo group patients treated with anti- infectives versus those that were not. The study will focus on the following diseases, including Parkinson's disease, Alzheimer's disease, Frontotemporal Dementia (FTD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), Migraine, Fibromyalgia and Systemic Lupus Erythematosus (SLE) in this project and future projects may be expanded to other neurological conditions. The knowledge obtained from this study will provide further data regarding the possible infection mechanisms involved in the pathogenesis of neurological disease, and whether anti-infective therapy may affect subsequent neurological disease processes. As a result these findings may offer potential avenues for diagnosing and treating neurological conditions, and positively modify their evolution.

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

We will identify whether individuals receiving anti-infective medications demonstrated any alterations in progression of the neurological condition they have been diagnosed with. The precise measure of disease progression will depend on the measures and outcomes available in the database. We will classify disease progression measures based on objectives, external measures, e.g. biochemical measures, behavioral measures, neurological, clinical, biomarkers, cellular function, and imaging data. We will examine whether there is a statistically lower level of disease impact and representation in individuals administered with anti-invective treatment compared to individuals that were not provided with any such treatment throughout the study.
Attached is a table with all predictors that will be used per disease.
Change in outcome measure will be calculated as change from baseline to last observed value using LOCF methodology, and will classifies initially as improved, worsening or no change

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

For each clinical study, subjects demonstrating improvement on the efficacy outcome measures of the study will be considered to have positively responded to the anti-infective treatments in terms of their neurological condition.
Other independent variables that will used:
1. Concomitant medications taken will be classified by the pharmacological subgroup of medication in all 5 levels.
2. All Pharmacological levels of anti-infective concomitant medications with at least 30 patients.
Descriptive statistics on medications will include: Duration of treatment, total daily dose provided, and type of anti-infective agent given.
All these will be examined to determine whether these types of medication alter neurological disease outcome. In addition, we are interested to explore whether different types of microbial infection may alter neurological disease progression. Based on the availability of data, this will be examined in the study.

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

We will collect demographic data, baseline characteristics of their disease. This data will be used to analyze the data and look on descriptive statistics on each group of patients analyzed.

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

Statistical Analysis Plan:

A Detailed Statistical Analysis Plan (SAP) compiled upon exploration of the available data and applied in SAS on the Vivli Platform.
The Plan will include the following key parameters:
1. Only patients from the placebo group will be used for each clinical trial.
2. Studies with a minimum of 100 participants, will be included.
3. Placebo group patients will be split into 2 groups, those that were provided anti-infective medications (for study -unrelated reasons) and those that were not (further details below).
4. Separate analysis will be performed for each neurological disease and each study.
5. Efficacy outcome measures (i.e. endpoint) will be used for each study to classify the patients as improved, no change or worsened for that specific outcome measure.
6. Change in outcome measure will be calculated as change from baseline to last observed value using LOCF methodology.
7. Early termination patients will be excluded from the analysis in order to compare changes on the same time scale.
8. The following analyses will be done for each study and each efficacy outcome measures separately:
a. Top level pharmacological subgroup medications will be assessed first.
b. Chai-Square (2x3) test will be performed to calculate the significant effect on anti-infective treated vs untreated with regard to change in disease progression.
c. Descriptive statistics will be used to analyzed the group of patients included in the Study, duration, patient medical history, baseline characteristics and disease related prognostic factors.
d. The pharmacological group will be further split down into subgroups (e.g., antibiotics, antivirals, anti-fungals, etc.).
e. Steps a to d will be repeated by further splitting down the pharmacological groups as the data allows.
f. Splitting will be stopped when all subgroup of pharmacological group are below 30 patients.
9. Following the completion of each study we will try to combine several clinical data sets from multiple studies on same disease each outcome measure separately and perform step 7 again on the combined data
Software Used:
Python

Project Timeline:

1. Understanding data content, structure, completeness and relationship between data elements (6 weeks)
2. Build a detailed statistical analysis plan (3 weeks)
3. Analyze each study separately (3-4 weeks), in total 7-9 months to complete the analysis
4. Meta-analysis (1 month)
5. Statistical report (1 month)
6. Publication (2 months)

Total project timeline approximately 12-14 months

Dissemination Plan:

Upon completion of the data analysis, study results will be shared with colleagues with the aim to establish a collaboration for further work in this area. Findings will also be written as a manuscript and submitted to appropriate journals (e.g., journal of Clinical Neuroscience, Neurology, Lancet Neurology, etc.) for publication based on the robustness and significance of the data. Findings may also be presented in distinguished conferences and congresses (e.g., American Academy of Neurology- AAN, European Academy of Neurology-EAN, World Congress of Neurology- WCN, etc.). If warranted, a request for access to further data will be made to examine interesting findings in more detail.

Bibliography:

Bibliography:
(1) Dehhaghi, M., Kazemi Shariat Panahi, H., & Guillemin, G. J. (2018, December 04). Microorganisms' Footprint in Neurodegenerative Diseases. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6288487/
(2) Wouk, J., Rechenchoski, D. Z., Rodrigues, B. C., Ribelato, E. V., & Faccin-Galhardi, L. C. (2021). Viral infections and their relationship to neurological disorders. Archives of Virology, 166(3), 733-753. doi:10.1007/s00705-021-04959-6

(3) Ma, Q., Xing, C., Long, W. et al. Impact of microbiota on central nervous system and neurological diseases: the gut-brain axis. J Neuroinflammation 16, 53 (2019). https://doi.org/10.1186/s12974-019-1434-3 . doi: https://doi.org/10.1186/s12974-019-1434-3
(4) Mallah, K., Couch, C., Borucki, D. M., Toutonji, A., Alshareef, M., & Tomlinson, S. (2020). Anti-inflammatory and Neuroprotective Agents in Clinical Trials for CNS Disease and Injury: Where Do We Go From Here?. Frontiers in immunology, 11, 2021. https://doi.org/10.3389/fimmu.2020.02021
(5) Mehnert, U. M. F. L. (2018). The Management of Urine Storage Dysfunction in the Neurological Patient.Datawyse / Universitaire Pers Maastricht. https://doi.org/10.26481/dis.20181213um https://www.who.int/mental_health/neurology/neurodiso/en/
(6) Desforges, Marc et al. “Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System?.” Viruses vol. 12,1 14. 20 Dec. 2019, doi:10.3390/v12010014
(7) Gravina, Antonietta Gerarda et al. “Helicobacter pylori and extragastric diseases: A review.” World journal of gastroenterology vol. 24,29 (2018): 3204-3221. doi:10.3748/wjg.v24.i29.3204
(8) Góralska, Katarzyna et al. “Neuroinfections caused by fungi.” Infection vol. 46,4 (2018): 443-459. doi:10.1007/s15010-018-1152-2
(9) Wouk, Jéssica et al. “Viral infections and their relationship to neurological disorders.” Archives of virology vol. 166,3 (2021): 733-753. doi:10.1007/s00705-021-04959-6
(10) Holmes, Aleah et al. “Gut dysbiosis and age-related neurological diseases; an innovative approach for therapeutic interventions.” Translational research : the journal of laboratory and clinical medicine vol. 226 (2020): 39-56. doi:10.1016/j.trsl.2020.07.012
(11) Galland, Leo. “The gut microbiome and the brain.” Journal of medicinal food vol. 17,12 (2014): 1261-72. doi:10.1089/jmf.2014.7000
(12) Sasmita, Andrew Octavian. “Modification of the gut microbiome to combat neurodegeneration.” Reviews in the neurosciences vol. 30,8 (2019): 795-805. doi:10.1515/revneuro-2019-0005
(13) Tyler Patterson, T, and Ramesh Grandhi. “Gut Microbiota and Neurologic Diseases and Injuries.” Advances in experimental medicine and biology vol. 1238 (2020): 73-91. doi:10.1007/978-981-15-2385-4_6
(14) Stock, Matthew L et al. “Antibiotics acting as neuroprotectants via mechanisms independent of their antiinfective activities.” Neuropharmacology vol. 73 (2013): 174-82. doi:10.1016/j.neuropharm.2013.04.059
(15) Stock, Matthew L et al. “Antibiotics acting as neuroprotectants via mechanisms independent of their antiinfective activities.” Neuropharmacology vol. 73 (2013): 174-82. doi:10.1016/j.neuropharm.2013.04.059
(16) Moir, R. D., Lathe, R., & Tanzi, R. E. (2018). The antimicrobial protection hypothesis of Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association, 14(12), 1602–1614. https://doi.org/10.1016/j.jalz.2018.06.3040

Supplementary Material:

https://yoda.yale.edu/sites/default/files/disease_main_predictors_list_by_disease.docx
https://yoda.yale.edu/sites/default/files/vivli_list_of_studies_in_addtion_to_yoda_list.docx
https://yoda.yale.edu/sites/default/files/supplement_-_full_abstract.docx