SRTP - Project Description Form #245

PART I:

Name of Schulich faculty member who will supervise the project	Juan Racosta
Supervisor's Schulich, Western, Hospital or Lawson Email	Juan.Racosta@lhsc.on.ca
Schulich Department	Clinical Neurological Sciences

PART II - Project Description

Title of Project	Investigating the association between drivers of disability accrual and progression independent of relapse activity (PIRA) and Relapse-Associated Worsening (RAW) in people living with multiple sclerosis (MS).

Background

Multiple sclerosis (MS) is a chronic immune-mediated disease that impacts the brain, spinal cord, and optic nerves. In people living with MS (pwMS), the immune system attacks myelin sheath, which leads to interruption of nerve signals. As MS is a leading cause of physical disability in young adults, it is important to better understand the ways in which pwMS acquire disability and characterize the drivers of worsening. MS is currently classified into 3 phenotypes, namely relapsing-remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS). While current disease modifying therapies are effective in RRMS, they have a small effect on SPMS and PPMS. This suggests that more needs to be understood about how to manage progression independent of relapses, taking place in these phenotypes. Recent studies by Kappos et al. (2020) and Lublin et al. (2022) have challenged the conventional classification system and alternatively proposed two distinct phenotypes of disability accrual in MS: Relapse-Associated Worsening (RAW) and Progression Independent of Relapse Activity (PIRA). Despite PIRA has been demonstrated to be significantly more prevalent than RAW in pwMS, the quantification of the amount of disability contributed by PIRA and RAW, has not been investigated yet. New understanding of the underlying drivers of disability explaining PIRA and RAW, as well as quantifying the amount of disability contributed by each phenomenon is likely to have important implications in defining treatment targets.

Hypothesis

The null hypothesis of our study is that there is no difference on the drivers of disability in the pwMS experiencing PIRA vs RAW. The second null hypothesis is that PIRA and RAW contribute similar amounts of disability to pwMS experiencing it.

Proposed Methodology

Participants: Between 2006 and 2023, longitudinal data from 3208 patients were collected from a single-centre (London Multiple Sclerosis Clinic) in Southwestern Ontario.

Study Design: Retrospective cohort study. Analysis of patient data from an established longitudinal database of people with MS and related demyelinating disorders in London, Ontario (MuSicaL). The MuSicaL database includes data from 3208 patients diagnosed with MS and related conditions, currently followed in the MS Clinic since 2006.

Variables: PIRA and RAW events will be defined according to Kappos et al.'s criteria, where progression was measured using the Expanded Disability Status Scale (EDSS). Disability determinants are extracted from patient records in the

MuSicaL database, including physical exam findings, symptom presentations.

Statistical Analyses: Statistical Analyses will be carried out using R. Patient demographics will be assessed with univariate descriptive statistics. Bivariate analyses between patient demographics and the disability determinants, and between patient demographics and presence of new lesions will also be conducted. Multivariable logistic regression will be used to assess the association between disability determinants and clinical course, adjusting for age, gender, and comorbidities.

Expected Outcomes

Expected Outcome 1. Identify disability determinants that drive disease progression in patients with PIRA and RAW.
We will analyze the prevalence of six categories as determinants of disability progression in the instances that pwMS present with PIRA and/or RAW : motor, coordination, visual, cognition, sensory impairment, and extraocular.

Expected Outcome 2. Quantify and compare the amount of worsening/disability in patients with PIRA and RAW.
To quantify the amount of disability worsening in the subgroups with PIRA and RAW, calculate the average EDSS score of PIRA patients in each subgroup (one subgroup = one disability determinant). Calculate the average EDSS score of RAW patients in each subgroup (one subgroup = one disability determinant). Compare between different disability determinant groups among PIRA and RAW populations.

Research Environment – Description of the number of research personnel, primary location of research, size of lab, etc

The total number of research personnel involved in this project will be 4. This project will be supervised by myself (Dr. Juan Racosta) and will be led by a first year medical student (Erin Lin). She will collaborate with the research coordinator (Samin Ayromlu). She will also consult the computer science student (Manav Preet Singh) for any queries regarding data extraction. The work and routine meetings will be conducted remotely.

Names and titles of other individuals who will be involved with the research project?

Juan Racosta, Assistant Professor
Erin Lin, First year Medical Student
Samin Ayromlu, Research Coordinator
Manav Preet Singh, Computer Science Student

Can this project be done remotely?	Yes
Duration of Project	Two Summers

Expected Objectives/Accomplishments for Student for Year 1?

1. Literature Review and Problem Definition:
Conduct a comprehensive literature review to understand the current state of research in the field of PIRA, RAW, and MS.
Clearly define the research problem or question that the project aims to address.

2. Formulating Hypotheses or Research Questions:
Develop testable hypotheses or specific research questions based on the identified research problem.

3. Research Design and Methodology:
Design a robust research methodology that aligns with the objectives and hypotheses.
Select appropriate data collection methods and tools (e.g., R studio).
Create a timeline for data collection, analysis, and interpretation.

4. Data Collection
Extract from MuSicaL database and identify disability determinants that drive disease progression in patients with PIRA and RAW.
Extract EDSS scores and populate into subgroups.

Ensure the quality and reliability of the collected data.

5. Preliminary Data Analysis:
Conduct initial data analysis to identify trends, patterns, or outliers.
Modify the research design or data collection strategy based on the preliminary findings if necessary.

6. Methodological Refinement:
Evaluate the effectiveness of the research methodology used in the first summer.
Make necessary adjustments or refinements to improve the study's rigor and validity.

SRTP-specific: Submit an abstract to Schulich at the end of the first summer.

Expected Objectives/Accomplishments for Student for Year 2?

1. Data Analysis:
Perform in-depth data analysis using appropriate statistical or qualitative methods.
Patient demographics will be assessed with univariate descriptive statistics.
Bivariate analyses between patient demographics and the disability determinants, and between patient demographics and presence of new lesions will also be conducted.
Multivariable logistic regression will be used to assess the association between disability determinants and clinical course, adjusting for age, gender, and comorbidities.
Interpret the results in the context of the research questions or hypotheses.

2. Results Presentation:
Prepare clear and concise presentations of the research findings.
Consider the most suitable formats for dissemination, such as papers, presentations, or visualizations.

3. Manuscript Writing:
Write a research manuscript summarizing the study, methods, results, and conclusions.

4. Feedback, Revision, and Submission:
Gather feedback from peers, mentors, or reviewers.
Revise the research paper based on feedback.
Submit the paper to relevant conferences or journals for publication.

5. Documentation and Archiving:
Document the research process, methods, and findings thoroughly for future reference.
Archive data and materials to ensure reproducibility and transparency.

6. Presentation and Dissemination:
Present the research findings at conferences, seminars, or other relevant forums.

7. Reflection and Future Directions:
Reflect on the research project, considering its strengths, limitations, and areas for improvement.
Identify potential avenues for future research or extensions of the current study.

SRTP-specific: Submit a report to Schulich at the end of the second summer.

PART III - Certifications

If the project will require any certification approvals from one or more of the following offices, please check the appropriate box below.	- Human Ethics

Human Ethics: If you have the protocol information, please enter it below (or

enter the status of the approval). HSREB: 121763

Note: certification approval should be obtained prior to the start of the summer. Projects without this approval will not be a priority for funding.