COVID-19 in MS

Global Data Sharing Initiative (GDSI)

Analyses plan 2021

Version 1 - last update 20th of May 2021

Aim of this document

This document serves to inform the GDSI partners about our proposed analyses plan, timelines and expected results for 2021. Everything in this document is open for discussion, so please come back with your input and feedback. You can reach out to Lotte Geys (lotte.geys@uhasselt.be) at all times.

Overall objectives of 2021

In 2021, we aim to focus on the following major objectives:

1. Re-run the previous analyses plan to confirm and/or re-evaluate our previous findings
2. Fine-tune the previous analyses plan so we can address some research questions in more detail and potentially explain some of the findings
3. Expand our previous analyses plan in order to address new research questions

Approach and timing

The supporting slide deck used during the data partners meeting of the 18th of May summarizes our approach and timelines. The slides can be consulted using this link.

Re-run the analyses plan 2020

Here, we aim to confirm and/or re-evaluate our previous findings. Consult our pre-print for more information.

Specific questions we aim to address here are:

- Can we re-assess the value of patient-reported data to confirm the insights gathered using clinician-reported data now that COVID-19 testing has become broadly available?
- Do the earlier signals increase/remain stable/decrease when the numbers increase?
- Consider using glatiramer acetate (GA) as control instead of dimethyl fumarate (DMF) (assuming we will now have a non-zero number of outcomes on GA)
- Can we evaluate the effect of some DMT's on the severity of COVID-19 outcomes that we could not address before because of the limited number of records?

To address these questions:

- no major changes to the Analyses Plan 2020 are required.
- **important note:** we have *fine-tuned* the script so we only query the data we really need for downstream analyses. Last year, we explored more options to define the final model. To reduce the privacy risk of the federated pipeline, we have eliminated many of these queries. This document only summarizes the scripts that will be leveraged into 2021.
- we should be able to complete all of this in "analyses round 1" leading up to the ECTRIMS late breaker

Fine-tune the previous analyses plan

We aim to address some research questions in more detail and potentially explain some of the findings.
Specific questions we aim to address here are:

- Can we increase the power of our calculations by introducing a “multi-level” COVID-19 outcome (e.g. no hospitalisation - hospitalisation but no ICU - ICU admission but recovered - death) instead of looking at the different outcome separately?
- Is the effect of a DMT influenced by the duration of treatment at time of COVID-19 onset? If so, can this potentially explain the difference in the signals observed for rituximab versus ocrelizumab?
- What happens if we include additional potentially relevant confounding variables in our model (e.g. co-morbidities, smoking, …)?

Question	Approach Round 1	Approach Round 2

Can we increase the power of our calculations by introducing a "multi-level" COVID-19 outcome instead of looking at the different outcome separately?	**Introduce new variable "covid19_outcome_levels_1"**
	covid19outcome_levels=0 if covid19_admission_hospital = No;
	covid19outcome_levels=1 if covid19_admission_hospital = yes AND [covid19_icu_stay = no OR covid19_ventilation=no]
	covid19_outcome_levels=2 if covid19_icu_stay = yes OR covid19_ventilation=yes
	covid19_outcome_levels=3 if covid19_outcome_death = yes
	
	Introduce new variable "covid19_outcome_levels_2"
	covid19outcome_levels=0 if covid19_admission_hospital = no;
	covid19outcome_levels=1 if covid19_admission_hospital = yes;
	covid19_outcome_levels=2 if covid19_icu_stay = yes OR covid19_ventilation=yes;
	covid19_outcome_levels=3 if covid19_outcome_death = yes;
	
	Note: we are working with these two different variants of the covid19_outcome_levels because in our analyses round 1 we are exploring what is the best approach
	● covid19_outcome_levels_1 is more clinically relevant (and correct)
	● covid19_outcome_levels_2 will lead to less missingness in the outcome measure
	
	ADD covid19outcome_levels as an outcome measure
		To be defined - updates on the approach will follow shortly

Is the effect of a DMT influenced by the duration of treatment at time of COVID-19 onset? If so, can this potentially explain the difference in the signals observed for rituximab versus ocrelizumab?	**Introduce new variable "duration_treatment"** (=number of days between start of treatment and date of onset covid19) duration_treatment = covid19_date_suspected_onset - dmt_start_date; **Introduce new variable "duration_treatment_cat1"** duration_treatment_cat1 = <1 = 0 duration_treatment_cat1 = between 1 and 2 years = 1 duration_treatment_cat1 = >2 years = 2 **Introduce new variable "duration_treatment_cat2"** duration_treatment_cat2 = <6m duration_treatment_cat2 >6m **Note**: we are working with these two different variants of the duration_treatment_cat because in our analyses round 1 we are exploring what is the best approach ● duration_treatment_cat1 has been defined using the preliminary results of the Swedish Registry in mind ● duration_treatment_cat1 has been defined based on the pre-existing categorisation of within the US cohort (one of our largest cohort) and to allow optimal alignment with the other cohorts **Add duration_treatment_cat as risk factor**	***To be defined - updates on the approach will follow shortly***

What happens if we include additional potentially relevant confounding variables in our model (e.g. co-morbidities, smoking, …)?	**Add one single risk factor as risk factor**	***To be defined - updates on the approach will follow shortly***

Expand our previous analyses plan

Here, we aim to new research questions

- Is there a difference in severity of outcomes between the first and second COVID-19 wave?
- Does the likelihood of COVID-19 infection after vaccination vary by DMT type?
- Once vaccinated, what are the characteristics of COVID-19 severity, particularly DMT type?

Research question	Approach Round 1	Approach Round 2
Is there a difference in severity of outcomes between the first and second COVID-19 wave?	**Introduce new variable "covid_wave" in two ways:** **Covid_wave1** Have the registry categorize it themselves and provide us with the definition **Covid_wave2** using hard cuts (real first wave 1, real first wave 2) covid_wave2 = 1 when covid19_date_suspected_onset before 31st of May 2020 covid_wave2 = 2 when covid19_date_suspected_onset after 1st of October 2020 **Note**: we are working with these two different variants of the covid_wave because in our analyses round 1 we are exploring what is the best approach ● covid_wave1 does not reduce the number of records, but might results in reviewer and community comments on the intuitive categorization and heterogeneity across the cohorts ● covid_wave2 could reduce the number of records, but provides us with a more clearer "cut" between what can be referred to a the 'real first wave' and the 'real second wave' at global scale. **Add covid_wave as risk factor (similar to stated above)**	***To be defined - updates on the approach will follow shortly***
Does the likelihood of COVID-19 infection after vaccination vary by DMT type?	***Not applicable (analyses on vaccination are delayed > october)***	***Not applicable (analyses on vaccination are delayed > october)***
Once vaccinated, what are the characteristics of COVID-19 severity, particularly DMT type?	***Not applicable (analyses on vaccination are delayed > october)***	***Not applicable (analyses on vaccination are delayed > october)***

Summary

In summary, the following frequency request will be used in the federated registries to run the analyses in “analyses round 1”

BY report_source
AND BY covid19_diagnosis
AND BY covid19_admission_hospital or covid19_icu_stay or covid19_ventilation or covid19_outcome_death or covid19_outcome_ventilation_or_ICU covid19outcome_levels1 covid19outcome_levels2
AND BY dmt_type_overall
AND BY by age_in_cat
AND BY ms_type2
AND BY sex_binary
AND BY edss_in_cat2
AND BY one of the following variables:

- current_or_former_smoker
- bmi_in_cat2
- Disease_duration_in_cat2
- dmt_glucocorticoid
- has_comorbidities
- duration_treatment_cat1
- duration_treatment_cat1
- covid_wave1
- covid_wave2