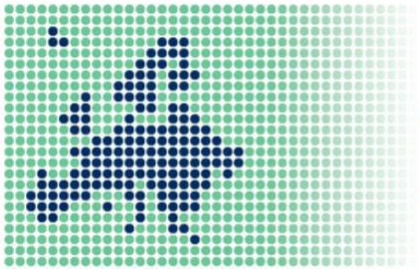

neatid The European treatment network for HIV, hepatitis and global infectious diseases

STATISTICAL ANALYSIS PLAN

Protocol Title:	**A MULTI-CENTRE, MULTI-COUNTRY RETROSPECTIVE COHORT STUDY TO EVALUATE THE CLINICAL OUTCOMES IN ADULTS WITH COVID-19 WHO HAVE BEEN TREATED WITH REMDESIVIR**
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1. Abbreviations and Definitions

Acronym	Description
ALT	Alanine Amino Transferase
AST	Aspartate aminotransferase
COPD	Chronic obstructive pulmonary disease
COVID	Coronavirus disease
CV	Cardiovascular
DM	Demographic
ECMO	Extracorporeal membrane oxygenation
e-CRF	Electronic Case Report Form
EMR	Electronic Medical Record
HIV	Human Immunodeficiency virus
ICU	Intensive Clinical Unit
ITU	Intensive Terminal Unit
NEAT ID	The European treatment network for HIV, hepatitis and global infectious diseases
NEWS	National Early Warning Score
NK	Not Known
ORDSC	Ordinal Scale Category
PCR	Polymerase Chain Reaction

2. Statistical hypothesis

There is no formal statistical hypothesis to be tested in these analyses. The study will explore the clinical course and outcome of adults with COVID-19 who have been treated with Remdesivir.

3. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
All-cause mortality at Day 28	• Occurrence of death (all cause) within 28 days
Secondary	
1. a 7-point ordinal clinical status scale on Day 7, 14 and 28 (or at last observation if discharged or died prior to this time point) 2. clinical severity at Day 7, 14, 28 as assessed by the NEWS 2 score 3. SpO2 > 94% on room air on day 7, 14 and 28 4. duration and type (low versus high flow) of oxygen therapy (days) 5. admitted to ICU (yes versus no) 6. number of days spent on ICU/ITU 7. use of mechanical ventilation/ECMO (extracorporeal membrane oxygenation); start and stop dates 8. duration of hospitalisation 9. timing (from first symptoms and from hospitalisation) and duration of use of Remdesivir 10. re-admission with COVID-19 complications or recurrence within 28 days of discharge and outcome (discharged or deceased)	1. Disease state on a 7-point scale defined as 1. death, 2. hospitalised, on invasive mechanical ventilation or ECMO, 3. hospitalised, on non-invasive ventilation or high flow oxygen devices, 4. Hospitalised, requiring low flow supplemental oxygen, 5. hospitalised, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise), 6. hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care, 7. not hospitalised at Day 7 and 14, and 28 (or at last observation if discharged or died prior to this time point) 2. Occurrence of disease severity at day 7, 14, 28 as assessed by NEWS2 score 3. SpO2 on room air on day 7, 14, and 28 3.1. Occurrence of SpO2 >94% on room air on day 7, 14 and 28 3.2. Time to SpO2 >94% on room air 4. Oxygen therapy over the 28 days 4.1. Frequency of oxygen therapy overall and by type (low versus high flow oxygen) 4.2. Duration (days) of oxygen therapy 5. Frequency of ICU admission 6. Number of days spent in ICU/ITU 7. Mechanical ventilation over the 28 days

	7.1. Frequency of mechanical ventilation/ECMO 7.2. Time (days) on mechanical ventilation/ECMO 8. Duration (days) of hospitalisation 9. Timing of use of Remdesivir 9.1. Time (days) from first symptoms to use of Remdesivir 9.2. Time (days) from hospitalisation to use of Remdesivir 9.3. Duration (days) of use of Remdesivir 10. Re-admission within the 28 days following discharge 10.1. Frequency of re-admission with COVID-19 within 28 days of discharge 10.2. Frequency of discharge after re-admission 10.3. Frequency of death after re-admission

4. Study Methods

4.1 General Study Design and Plan

This is a multi-centre, multi-country retrospective cohort study. At least 450 COVID-19 cases from up to 20 participating study sites who meet all eligibility criteria will be included in the analysis.

Deidentified data will be extracted from electronic medical record (EMR) databases, clinical registries, case series or additional sources from participating sites and countries, and then entered into a structured e-CRF system. Addition, each site/country will be surveyed to determine the local standard of care therapy for COVID-19 infection and to determine if standard protocols were/are in place for the use of Remdesivir and if/how the protocols changed over time.

Number of Sites and Subjects Planned

Up to 20 centres with 450 cases of Covid-19 treated with at least one dose of Remdesivir

Target Population

Adults with COVID-19 diagnosed and treated with Remdesivir after Aug 31st 2020.

4.2 Study Variables

All the study variables are summarized in the following table.

	Day1 (Hospital Admission) baseline	**Day 7 (+/- 1 day) and Day14 (+/- 2 days) / last observation if discharged or died prior to these time points.**	**Day 28 or last observation after Day 14 if discharged or died prior to this time point.**
Medical History [a]	x		
Pregnancy test	x		
HIV test	x		
Vital Signs [b]	x	x	x
Laboratory Testing [c]	x	x	x
Oxygenation [d]	x	x	x
Clinical Status [e]	x	x	x
Other Treatments for COVID-19 [f]	x	x	x
NEWS SCORE [g]	x	x	x

a. Focused medical history and also the following information (e.g. demographics including ethnicity, baseline characteristics including DM, CV disease and COPD)
b. SpO2, body temperature, body weight and height on admission
c. Includes white blood cell count, creatinine, total bilirubin, ALT, AST at admission Day 7 and day 14 or at discharge if before day 14, radiographic findings at baseline and as available and SARS-CoV-2 PCR, antigen and/or antibody testing.
d. Includes oxygen supplementation: room air, low flow O2 (L/min and %), high flow O2 (L/min and %), non-invasive positive pressure ventilation (FiO2 or %), mechanical ventilation (FiO2 or %), ECMO (extracorporeal membrane oxygenation)
e. The ordinal scale is as: 1. Death, 2. Hospitalised, on invasive mechanical ventilation or ECMO, 3. Hospitalised, on non-invasive ventilation or high flow oxygen devices, 4. Hospitalised, requiring low flow supplemental oxygen, 5. Hospitalised, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise), 6. Hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care, 7. Not hospitalised
f. These include corticosteroids, anticoagulants, azithromycin/other antibiotics, anti-inflammatory agents (e.g. Tocilizumab), investigational agents (eg hydroxychloroquine) and immunotherapies such as convalescent plasma and monoclonal antibodies.
g. NEWS 2 score is based on Respiration rate (per minute), SpO2 (%) Air or oxygen. Systolic blood pressure (mmHg), Pulse (per minute) Consciousness, Temperature (°C)

For the purpose of the analyses, partial dates will be extrapolated. For example, all dates saved as NK/FEB/2020 will be recoded as 15/FEB/2020 and those saved NK/NK/2020 will be recoded as 15/JUNE/2020. NK means not known.

5. Sample Size calculation

This is a non-interventional, observational study where no formal samples size calculation is to be performed. It is anticipated that at least 450 adults with COVID-19 and treated with Remdesivir could be recruited across centres from NEAT ID Network.

6. General Considerations

6.1 Timing of Analyses

An interim analysis is planned to be performed in June 2021.

The final analysis will be performed in July-September 2021.

6.2 Analysis Populations

All enrolled participants who met the eligibility criteria and with data available at baseline will be included in the Full Analysis Population. The primary endpoint and all secondary endpoints will be analysed on this Full Analysis population.

7. Summary of Study Data

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, 1st quartile, median, 3rd quartile, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical variables.

7.1 Subject Disposition

The number of patients and the flowchart of the study will be presented. The period of enrolment will be given. The number of patients excluded, and the total number of analysed patients will be presented. The number of patients who never take the study treatment will also be given. The number of patients who did not receive the full dose of Remdesivir will also be presented. The number of participants who discharge or die before day 28 will be presented.

7.2 Demographic and baseline variables

The baseline patients' characteristics of the full analysis population will be described globally and according to the Ordinal Scale (ORDSC) clinical status at baseline (score 2 vs 3-4 vs 5)

and will be presented in a summary table. The summary statistics will be produced in accordance with section 7. Non-parametric Kruskal-Wallis test will be used to compare continuous variable between the 3 groups and Chi-square test for categorical variables. P-values will be two-tailed with a significant level at 5%.

This table will be structured as follows:

8. Efficacy Analyses

8.1 Primary Efficacy Analysis

Primary endpoint	• **Occurrence of death within 28 days**
Analysis population	• Full population analysis
Descriptive statistics and graphical representation	• Data will be summarized with proportion and 95% confidence interval globally and according to disease severity at baseline (ORDSC score 2 vs 3-4 vs 5) • LogRank test will be used to compared the 3 groups • P-values will be two-tailed with a significant level at 5%. • Kaplan-Meier curves will be plotted
Statistical analysis	Kaplan-Meier estimates will be used to calculate the proportions and the 95% confidence intervals Time to death will be defined as the time between the date of hospitalization and the date of death or discharge from hospital or last observation Participant with missing clinical status or alive at day 28 will be censored at the date of last observation

8.2 Secondary Efficacy Analyses

Endpoint	**1. Disease state on a 7-point scale at Day 7, 14 and 28 (or last observation if discharged or died prior to this time point) defined as:** 1. death, 2. hospitalized, on invasive mechanical ventilation or ECMO, 3. hospitalized, on non-invasive ventilation or high flow oxygen devices, 4. Hospitalized, requiring low flow supplemental oxygen, 5. hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise), 6. hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care, 7. not hospitalized

Analysis population	• Full population analysis
Descriptive statistics and graphical representation	• Data will be summarized with proportion and 95% confidence interval globally and according to disease severity at baseline (ORDSC score 2 vs 3-4 vs 5) • Proportional odds models will be used to compared the 3 groups • P-values will be two-tailed with a significant level at 5%.
Statistical analysis	The proportions will be calculated by the number of subjects in each category divided by the total number of subjects in the full analysis population. Subjects with missing clinical status will be considered deceased The associated two-sided 95% exact confidence intervals will be calculated using Clopper–Pearson method

Endpoint	**2. Disease severity at day 7, 14, and 28 as assessed by NEWS 2 score**
Analysis population	• Full population analysis
Descriptive statistics and graphical representation	• Data will be summarized with mean and 95% confidence interval globally and according to disease severity at baseline (ORDSC score 2 vs 3-4 vs 5) • Linear mixed models will be used to compared the 3 groups • P-values will be two-tailed with a significant level at 5%. • The evolution curves will be plotted
Statistical analysis	The changes from baseline in NEWS 2 score within group will be compared using mixed models for repeated measures with random intercept and unstructured covariance matrix, adjusted for baseline value. Subjects who die will be imputed as a score of 20 and subjects who are discharged will be imputed a score of 2. The sample size is quite large to consider the residuals of the mixed model is normally distributed. Time will be considered as categorical variable

Endpoints	**3.1. Occurrence of SpO2 >94% on room air on day 7, 14 and 28** **3.2. Time to SpO2 > 94% on room air**
Analysis population	• Full population analysis
Descriptive statistics and graphical representation	• Data will be summarized with proportion and 95% confidence interval for the occurrence of SpO2 >94% on room air and median and 95% confidence interval for time to Sp02>94%. • Data will be summarized globally and according to disease severity at baseline (ORDSC score 2 vs 3-4 vs 5)

	• LogRank test will be used to compared the 3 groups • P-values will be two-tailed with a significant level at 5% • Kaplan-Meier curves will be plotted
Statistical analysis	Kaplan-Meier estimates will be used to calculate the proportion and the median time as well as the associated 95% confidence intervals Time to event will be defined as the time between the date of first symptom and the date of the event of interest or hospital discharge or last observation Subjects who died with SpO2 ≤94% will be censored at day 28

Endpoints	**4.1. Frequency of oxygen therapy overall and by type (low versus high flow oxygen)** **4.2. Duration (days) of oxygen therapy** **5. Frequency of ICU admission** **6. Number of days spent in ICU/ITU** **7.1. Frequency of mechanical ventilation/ECMO of hospitalization** **7.2. Time on mechanical ventilation/ECMO**
Analysis population	• Full population analysis
Descriptive statistics and graphical representation	• Data will be summarized with proportion or median and 95% confidence interval according to the endpoint • Data will be summarized globally and according to disease severity at baseline (ORDSC score 2 vs 3-4 vs 5) • LogRank test will be used to compared the 3 groups • P-values will be two-tailed with a significant level at 5% • Kaplan-Meier curves will be plotted
Statistical analysis	Kaplan-Meier estimate will be used to estimate the proportion of subject with oxygen therapy and by type (low versus high flow oxygen), the proportion of subjects admitted in ICU and the proportion of those having received mechanical ventilation or ECMO. Time to event will be defined as the time between the date of first symptom and the date of event of interest. Participants not experienced the event of interest will be censored at last observation date. Participants who deceased before will be considered as having the event. The duration (days) of oxygen therapy, the number of days spent in ICU/ITU and the time (days) on mechanical ventilation/ECMO will be estimated using Kaplan-Meier estimates as well as the associated 95% confidence intervals. The time will be defined as the time between the start date of event and the end date of the event of interest or hospital discharge. Subjects who died will be censored at day 28.

Endpoint	**8. Duration (days) of hospitalization**

Analysis population	• Full population analysis
Descriptive statistics and graphical representation	• Data will be summarized with median and 95% confidence interval globally and according to disease severity at baseline (ORDSC score 2 vs 3-4 vs 5) • LogRank test will be used to compared the 3 groups • P-values will be two-tailed with a significant level at 5% • Kaplan-Meier curves will be plotted
Statistical analysis	Kaplan-Meier method will be used to calculate the medians and the 95% confidence intervals. Time (days) from hospitalization to hospital discharge will be defined as the time between the date of hospitalization for COVID-19 and the date of hospital discharge. The event will be hospital discharge. Subjects who died will be censored at day 28.

9. Other Analyses

Endpoints	**9.1. Time (days) from first symptom to use of Remdesivir** **9.2. Time (days) from hospitalization to use of Remdesivir** **9.3. Duration (days) of use of Remdesivir**
Analysis population	• Full population analysis
Descriptive statistics and graphical representation	• Data will be summarized with median and 95% confidence interval globally and according to disease severity at baseline (ORDSC score 2 vs 3-4 vs 5) • LogRank test will be used to compared the 3 groups • P-values will be two-tailed with a significant level at 5% • Kaplan-Meier curves will be plotted.
Statistical analysis	Kaplan-Meier method will be used to calculate the medians and the 95% confidence intervals of the time to use of Remdesivir. Time (days) from first symptom to use of Remdesivir will be defined by the time between the date of first symptom and the start date of Remdesivir. The event will be the exposure to Remdesivir therapy at least one time during the hospitalization period The time (days) from hospitalization to the use of Remdesivir will be estimate using the Kaplan-Meier method as well as the 95% confidence interval. The event will be the first use of Remdesivir. Duration (days) of use of Remdesivir will be estimated using the Kaplan-Meier method. The time is defined as the time between the start date of Remdesivir and the end date of Remdesivir. The event will be the discontinuation of the use of Remdesivir.

Endpoints	**10.1. Frequency of re-admission with COVID within 28 days of discharge** **10.2. Frequency of discharge after re-admission** **10.3. Frequency of death after re-admission**
Analysis population	• For 10.1, the analysis population will be all subjects who discharge from hospital within the first 28 days • For 10.2 and 10.3, the analysis population will be all re-admitted subjects
Descriptive statistics and graphical representation	Data will be summarized with number of subjects with an event out of the total number of analyzed population Data will be summarized globally and according to disease severity at baseline (ORDSC score 2 vs 3-4 vs 5) Chi square test will be used to compared the 3 groups P-values will be two-tailed with a significant level at 5%
Statistical analysis	The frequency will be estimated by the number of events divided by the total number of analyzed population. . The associated two-sided 95% exact confidence intervals will be calculated using Clopper–Pearson method

11. Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

12. Technical Details

Data will be analysed using the IBM SPSS® statistics software version 24, Stata® SE software version 13 and SAS® software version 9.4.

Appendix

Table 1: Baseline characteristic of participants and according to the disease severity at baseline

			Ordinal Scale Category at baseline Overall and by disease severity			
		Total N=xxx	**ORDSC score 2 N=xxx**	**ORDSC score 3-4 N=xxx**	**ORDSC score 5 N=xxx**	**P-value**
Age (years), median (IQR)						
Gender, n (%)	Male					
	Female					
Pregnant women, n(%)						
Ethnicity, n(%)						
	White caucasian					
	White mixed					
	Asian					
	Black					
	African					
	Caribbean					
	Other					
Geographic origin, n(%)						
	European					
	Other					
Body mass index (BMI, kg/m^2), median (IQR)						
	Undeweight ((<18.5 kg/m^2), n(%)					
	Normal (18.5-25 kg/m^2)					
	Overweight (25.01-30 kg/m^2)					
	Obese (>30 kg/m^2)					
Comorbidities, n(%)						
	Cardiovascular Disease excluding Hypertension					
	Diabetes at baseline					
	Cardiovascular Disease excluding Hypertension					
	Hypertension					
	Asthma					
	COPD					
	Severe renal disease					
	Liver disease					
	HIV infection					
	Chemo/radiotherapy for cancer					
	Receiving Immuno-Suppressive Agent (Not for Cancer)					
	Dementia					
Biological parameters						
White blood cells (10^12/L), median (IQR)						
ALT (U/L) , median (IQR)						
AST (U/L) , median (IQR)						
Total Bilirubin (umol/L) , median (IQR)						
Creatinine (umol/L) , median (IQR)						

Creatinine clearance (eGFR) (mL/min), MDRD method, median (IQR)						
Virological results						
	Positive PCR test, n(%)					
	CT value, median (IQR)					
Specimen type, n(%)						
	Nasopharyngeal swab					
	Oropharyngeal swab					
	Other					
Imaging results, n(%)						
	Normal					
	Abnormal					
	Unknown					
Presence of Pulmonary Infiltrates, n(%)						
Imaging Method, n(%)						
	X-Ray					
	CT Scan					
	Other					
Clinical status - Ordinal Scale, n (%)						
	2 - Hospitalized, on invasive mechanical ventilation or ECMO					
	3 - Hospitalized, on non-invasive ventilation or high flow oxygen devices					
	4 - Hospitalized, requiring low flow supplemental oxygen					
	5 - Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)					
Temperature (°C), median (IQR)						
	Systolic Blood Pressure (mmHg), median (IQR)					
	Pulse Rate (per minute), median (IQR)					
SpO2 (%), median (IQR)						
Supplemental oxygen, n (%)						
	Room Air					
	Low Flow O2					
	High Flow O2					
	Non-Invasive Positive Pressure Ventilation					
	Mechanical Ventilation					
	ECMO (Extra-Corporeal Membrane Oxygenation)					
Consciousness, n(%)						
	Alert					
	Verbal					
	Pain					
	Unresponsive					

NEWS 2 score, median (IQR)						
	Low (score 0-4), n(%)					
	Medium (score 5-6)					
	High (score 7 or more)					
COVID Vaccination, n(%)						
Other treatment for COVID-19, n (%)						
	Corticosteroids					
	Tocilizimab/Sarilumab					
	Other COVID Treatment Related Drug					

Table 2. Primary and secondary outcomes

		Ordinal Scale Category			
	Overall Total N=xxx	**Score of 2 N=xxx**	**Score of 3-4 N=xxx**	**Score of 5 N=xxx**	**P-value**
Mortality over entire study period					
Number of deaths by Day 28					
Kaplan-Meier estimate of mortality by Day 28 – % (95% CI)					
Ordinal Scale at day 7 (±1 day) – no. (%)					
1					
2					
3					
4					
5					
6					
7					
Ordinal Scale at day 14 (±2 days) – no. (%)					
1					
2					
3					
4					
5					
6					
7					
Ordinal Scale at day 28 (±2 days) – no. (%)					
1					
2					
3					
4					
5					
6					
7					
Disease severity assessed by NEWS 2 Score at 7 days					
Total N					
Mean NEWS 2 Score at days 7 (95% CI)					
Disease severity assessed by NEWS 2 Score at 14 days					
Total N					
Mean NEWS 2 Score at days 14 (95% CI)					
Disease severity assessed by NEWS 2 Score at 28 days					

Total N					
Mean NEWS 2 Score at days 28 (95% CI)					
SpO2>94% over first 7 days					
Number of SpO2>94% by Day 7					
Kaplan-Meier estimate of by Day 15 – % (95% CI)					
SpO2>94% over first 14 days					
Number of SpO2>94% by Day 14					
Kaplan-Meier estimate of SpO2>94 by Day 14 – % (95% CI)					
SpO2>94% over entire study period					
Number of SpO2>94% by Day 28					
Kaplan-Meier estimate of SpO2>94 by Day 28 – % (95% CI)					
Median time to SpO2>94% (95% CI) - days					
Oxygen therapy over entire study period (low or high flow)					
Number of oxygen therapy by Day 28					
Kaplan-Meier estimate of oxygen therapy by Day 28 – % (95% CI)					
Median duration on oxygen therapy (95% CI) - days					
Low flow oxygen therapy over entire study period					
Number of low flow oxygen therapy by Day 28					
Kaplan-Meier estimate of low flow oxygen therapy by Day 28 – % (95% CI)					
High flow oxygen therapy over entire study period					
Number of high flow oxygen therapy by Day 28					
Kaplan-Meier estimate of high flow oxygen therapy by Day 28 – % (95% CI)					
ICU admission over entire study period					
Number of ICU admission by Day 28					
Kaplan-Meier estimate of ICU admission by Day 28 – % (95% CI)					
Median duration spent in ICU (95% CI) - days					
Mechanical ventilation|ECMO over entire study period					
Number of Mechanical ventilation|ECMO by Day 28					
Kaplan-Meier estimate of Mechanical ventilation|ECMO by Day 28 – % (95% CI)					
Median duration on Mechanical ventilation|ECMO (95% CI) - days					
Hospitalization					
Hospitalization no					
Median duration on hospitalization (95% CI) - days					
Remdesivir exposure					
Total N					
Median time from first symptom to use of remdesivir (95% CI) - days					
Median time from hospitalization to use of remdesivir (95% CI) - days					
Median duration of use of remdesivir (95% CI) - days					
Readmission					
Number of readmission within 28 days of discharge					

Proportion of re-admission within 28 days of discharge (95% CI)					
Proportion of discharge after readmission (95% CI)					
Proportion of death after readmission (95% CI)					