ISARIC 4C CCP-UK Remdesivir

Statistical Analysis Plan – Final

V 0.6 10/12/2020

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Date	19/11/2020	

1. Change Control

Updated SAP version no.	Section number changed	Description of change	Date changed

2. Approval and agreement

SAP Version Number being approved: 1.0

Trial Statistician

Name

Signed _____ Date _____

Senior Statistician

Name

Signed _____ Date _____

Clinical lead

Name

Signed _____ Date _____

3. Roles and responsibilities

Name	Affiliation	Role
Barbara Arch (BA)	Liverpool Clinical Trials Centre (LCTC), University of Liverpool	Study Statistician
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Professor MG Semple (CS)	Chief Investigator ISARIC WHO Clinical Characterisation Protocol UK and Covid-19 Clinical Information Network (CO-CIN).	Chief Investigator
Richard Jackson (RJ)	Liverpool Clinical Trials Centre (LCTC), University of Liverpool	Internal Statistical Reviewer
Michaela Brown (MB)	Liverpool Clinical Trials Centre (LCTC), University of Liverpool	Internal Statistical Reviewer
Dr Ewan Harrison (EH)	Professor of Surgery and Data Science and Honorary Consultant Surgeon, University of Edinburgh	External Statistical and Clinical Reviewer

BA, AJ, and ARH proposed the statistical analysis plan (SAP). BA drafted the SAP. AJ, RJ, EH and CS read, amended and approved the SAP.

4. List of abbreviation and definitions of terms

Abbreviation	
ASD	Absolute standard difference
CCP-UK	Clinical Characterisation Protocol UK
CO-CIN	Covid-19 Clinical Information Network
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
DCMO	Deputy chief medical officer
EAMS	Early Access to Medicine Scheme
ECMO	Extracorporeal membrane oxygenation
GCP	Good clinical practice
ISARIC 4C	Coronavirus Clinical Characterisation Consortium
NICE	National Institute for Health and Care Excellence
RDV	Remdesivir
SAP	Statistical analysis plan
SpO_2	Oxygen saturation
WHO	World Health Organisation

Contents

5. Statement of Compliance

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the pre-planned final analyses for the study. Version 1.0 was agreed prior to seeing any data. It is written using the template ST001TEM01, and incorporating recommendations for the writing of SAPs for observational studies made by Hiemstra *et al*[1]. These analyses will be performed by the study statistician.

All analyses are performed with standard statistical software (SAS v9.4 or later, and R v3.6 or later). The finalised analysis datasets, programs and outputs will be archived following Good Clinical Practice (GCP) guidelines and SOP GE012 Archiving procedures. The testing and validation of the statistical analysis programs will be performed following SOP ST001.

6. Background and Rationale

In the current COVID-19 pandemic, therapeutic treatments are being sought, in particular in the care of severe disease. Several therapeutic drugs licensed for use in the treatment of other conditions have been trialled in the treatment of COVID-19. One drug of key interest in the UK setting, is Remdesivir (RDV). This was made available on 26th May 2020 in the UK under the MHRA EAMS (Early Access to Medicine Scheme), and on 3rd July it was moved from EAMS status to being clinically commissioned, based on the evidence available at the time. An assessment of efficacy of RDV in the UK is now sought.

6.1. EAMS Background

The MHRA EAMS (Early Access to Medicine Scheme) is a form of compassionate use programme. EAMS aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. The scheme is voluntary and operates within the current regulatory structure. The MHRA requires that a Registry be utilised to support capture of the real-world outcomes of the use of an EAMS medicine in UK patients. Data captured through an EAMS are expected to be used to support cost effectiveness and commissioning discussions as the medicine is licensed and becomes available for routine clinical use in the UK.

The Deputy Chief Medical Officer (DCMO) for Her Majesty's Government has mandated that data on all patients that receive Remdesivir through the EAMS must be captured through the ISARIC 4C Clinical Characterisation Protocol UK (CCP-UK) case report forms (CRFs), as coordinated by the COVID-19 Clinical Information Network (CO-CIN). Completion of the mandatory fields of the ISARIC WHO CCP-UK CRFs is required, to support ongoing implementation, including determination of future drug allocations between NHS hospitals, and evaluation (link to forms).

The DCMO has commissioned an analysis of efficacy and safety based on the pragmatic data being collected by CO-CIN.

6.1.1. Remdesivir EAMS

Gilead Sciences has submitted RDV to the EAMS scheme as a treatment for hospitalised patients with severe COVID-19.

6.1.2. Post July 2020

EAMS status of RDV was withdrawn in July 2020, and it was clinically commissioned for use in the UK. This was following an evidence review[2] by the National Institute for Health and Care Excellence (NICE). The data collection initiated to evaluate RDV under EAMS has continued.

6.2. Clinical trial evidence

At the time of writing, results from two key clinical trials (ACTT-1[3 4], and SOLIDARITY[5 6]) have been published/publicised. The ACCT-1 trial was carried out between February 21 to April 19, 2020 – giving early evidence for RDV compared with placebo. SOLIDARITY ran from March 22 to October 4, 2020, which included a comparison of RDV with 'local standard of care'. These suggest that for patients that are hospitalised with COVID-19, who require additional oxygen, but who do not initially require ventilation: RDV is effective compared with placebo in (a) reducing time-to-recovery; (b) improving clinical status at 15 days; (c) improving 28-day mortality; but RDV is not effective compared with 'standard of care' in (d) reducing time-to-recovery; (e) improving 28-day mortality. Over time, standard of care has evolved, and this may in part explain the lack of the benefits of RDV observed in SOLIDARITY. Both trials reported no benefit of RDV for patients that were more seriously ill at baseline: those initially requiring ventilation.

7. Study objectives

This documents proposed an 'ideal-case' analysis to address the objectives below. As data are observational, it is accepted some aspects of data quality and sample size may make some parts of what is proposed infeasible. The analysis may need to be adapted, in the light of the data, but a record of all changes together with rationales will be documented in the Change Control (Section 1 above).

7.1. Primary Objective

Evaluation of the efficacy of RDV in reducing 14-day mortality in newly diagnosed, hospitalised, non-ventilated severe COVID-19 patients.

7.2. Secondary Objectives

Evaluation of the efficacy of RDV in improving other key outcomes such as speed of recovery, hospital stay, and clinical status over the 28-days post diagnosis in newly diagnosed, hospitalised, non-ventilated severe COVID-19 patients.

8. Study design

8.1. Overall study design

This is a prospective, observational non-interventional matched cohort study, within the ISARIC 4C CCP, of hospitalised patients with severe COVID-19. Patients treated with RDV will be compared with matched controls (or if this is infeasible, with all patients satisfying key inclusion/exclusion criteria – see below). The time-scale is from baseline to 28 days post baseline.

8.2. Treatments studied

The key treatment of interest is RDV, given to patients at the early stage of a COVID-19 infection who have a high probability of developing severe disease. Guidelines were in place for its use in the UK – it was recommended for newly hospitalised patients, no later than within 10 days of symptom onset, and only initiated in non-ventilated patients. Patients were recommended to receive 200mg on Day 1 of treatment, followed by 100mg daily for 4 days. An optional additional 5 days of 100mg daily was recommended till 29th September, but the wording changed over time:
26th May to 2nd June: "If a patient does not demonstrate clinical improvement"
3rd June to 28th September: "If a patient deteriorates and progresses to ventilation and/or ECMO treatment"
29th September onwards: "Ensure that clinicians prescribe a maximum treatment course of 5 days" – this was due to a disruption in supply of the drug. It is stated that some exceptions may receive additional doses, but these were undefined by the guidelines.

The comparison treatment is: Standard of care, without RDV.
NB: Standard of care evolved as knowledge of the disease and how to treat it evolved. Co-medication with the corticosteroids dexamethasone and hydrocortisone became recommended for some patients part-way through our study period – these are not expected to interact with RDV, and so we expect that RDV patients will have received these in the same way as non-RDV patients. The drugs Hydroxychloroquine and Chloroquine phosphate were not recommended as concomitant medications for RDV from 3rd September 2020.

8.3. Baseline: definition

We take a common baseline to be 'date of hospitalisation due to COVID'. It is important to note that this is not necessarily when RDV was initiated, though it is likely that it was administered soon after admission. The definition of baseline depends on the where the infection was acquired:

Community acquired COVID-19 i.e. admitted with symptoms consistent with COVID-19:

Baseline = Date of admission to hospital

For hospital acquired COVID-19 :

Baseline = Date positive COVID-19 test was collected

'Hospital acquired' is defined as: symptom onset at least 5 days after hospital admission.

8.4. Patient population studied

Inclusion/exclusion guidelines for RDV use changed slightly over time. The following criteria are designed to create a cohort of patients that would have been eligible to receive RDV from baseline. They apply for the whole study period, and will be used to define our analysis cohort:

8.4.1. Inclusion criteria

- Laboratory confirmed SARS-CoV-2 infection
- Hospitalised
- Aged ≥ 18 years[a] at baseline
- Requiring supplementary oxygen (SpO_2 ≤ 94%) at any time during 24 hours post baseline
- RDV initiated ≤ 24 hours post baseline (RDV group only)[b]

8.4.2. Exclusion criteria

- Requiring a high flow cannula, any ventilation or ECMO during first 24 hours post baseline[c]
- Pregnant
- Chronic kidney disease
- RDV initiated > 24 hours post baseline[d]
- Is a COVID-19 re-admission (was previously hospitalised for COVID-19)
- Missing Day 1 Daily Treatment CRF
- Missing 'Medication' section of the Outcome CRF

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a RDV was recommended in people aged 12 and over, and weighing over 40kg. Weight was not generally measured at baseline for practical reasons, so we have excluded children aged 12-17 in order to be sure that no-one in the control group was likely to weigh less than 40kg.

b This criteria is an ideal, to measure the effectiveness of RDV initiated close to baseline. If RDV is more routinely given later than this, we will either remove this criteria, or move the window of inclusion to say 3 days. Statistics describing when RDV treatment was initiated compared with baseline, will be presented.

c This subgroup will be analysed separately (see Section 19).

d See footnote b above.

8.5. Consent process

All endpoints defined in this study are derived from data that can be obtained from hospital records. As part of the ISARIC WHO clinical characterisation protocol, multiple time point biological sampling is also recorded prospectively – for this, consent from patients must be obtained. Use of biological data however, are beyond the scope of the objectives of this analysis plan.

8.6. Blinding

Neither clinicians nor patients are blinded to treatments allocated.

8.7. Definition of treatment groups

The analysis cohort will be split into two treatment groups: RDV and non-RDV. As the study is observational, allocation of treatment is decided by clinicians.
A matching process will be carried out to link RDV patients with non-RDV patients as follows:
A logistic regression with dependent variable RDV (Yes/No) will be fitted including the following covariates:

1. Month of baseline
2. Tier of participating centre (0 / 1 and 2)
3. Sex
4. Age
5. Broad ethnicity group (White / Asian / Black / Other)
6. Clinically extremely vulnerable status (Yes: Cancer / Yes: Severe respiratory condition / Yes: on immunosuppression therapy / Yes: Other / No)
7. Comorbidities: Diabetes (Y/N), Hypertension (Y/N), Obesity (Y/N), Chronic Cardiac disease (Y/N), CPD (Y/N), Asthma (Y/N)
8. Where COVID was acquired (Community / Hospital)
9. Admitted to HDU/ICU at baseline (Y/N)

Note: a pragmatic approach will be taken – the list above defines a best-case set of matching criteria; it may be necessary for categories to be collapsed to simplified discriminators (e.g. White vs Other ethnicity, or 'Total number of comorbidities'), should the model become over-parametrised. If possible, 2nd order interactions will be investigated, and if statistically significant, added to the model. All main effects will be retained in the model, even if not significant.

The fitted model will be used to calculate the probability of receiving RDV for each patient according to their baseline factors. The probability calculated is called their propensity score (PS). Boxplots will

be presented showing the distribution of PS in each treatment group. Patients who were given RDV will then be matched to a control patient / patients with a similar PS who did not get RDV, using a nearest neighbour matching algorithm and a pre-specified maximum difference in PS (calliper width) of 0.2 standard deviations. The ratio of RDV patients to controls may be 1:1 or higher – to a maximum of 1:4 (Rassen (2012)[7] suggests that 1:*n* matching leads to higher precision in estimating effect sizes, with a cost of a small increase in bias with increasing *n*). Controls are chosen without replacement, so may not be matched to more than one RDV patient.

The matched cohort will be checked for balance, by using the disease risk score diagnostic described by Stuart (2013)[8]: an underlying primary outcome risk score will be calculated using the following analysis dataset: all non-RDV patients satisfying inclusion/exclusion. The primary outcome will be modelled using logistic regression, and the following key risk factors will be fitted as covariates: sex, age, and number of comorbidities. (These are chosen from Knight 2020[9], and as being the most measurable for most members of the cohort.) The fitted model will be used to calculate a primary outcome risk score (RS) for each patient included in the matched cohort. The mean and SD of RS will be calculated for each treatment group. The groups will be checked for balance by calculating the absolute standardised difference in RS:

$$ASD_{RS} = \frac{|\overline{RS}_T - \overline{RS}_C|}{\sqrt{\frac{s_T^2}{2} + \frac{s_C^2}{2}}}$$

Where s_T and s_C are the standard deviation of RS in RDV and control groups respectively.

If $ASD_{RS} < 0.1$, the matching will be considered balanced.

If matching is found to have been unsuccessful in balancing treatment and control groups, the propensity score model will be revised.

Patients from either treatment group that are not matched will be excluded from inferential analyses, and will be described separately.

8.8. Sequence and duration of study periods

All patients are followed up until discharge, death, or 28 days post baseline – whichever occurs first.

8.9. Schedule of assessments

Data are collected on patients per the CCP-UK Tier Zero schedule and: on each day of RDV dosing, on day 14 after RDV initiation, then on death, discharge or day 28 post hospitalisation, depending which is soonest.

9. Listing of outcomes

9.1. Primary outcome

14-day mortality

9.2. Secondary Outcomes

Secondary outcomes are:

1. Time-to-recovery, where recovery is defined as: discharge from hospital or continued hospitalisation with no on-going health-care needs related to COVID-19
2. 28-day mortality
3. Time-to-death
4. Clinical status at day 15[e]
5. Length of time receiving supplementary oxygen
6. Time-to-first ventilation
7. Use of non-invasive ventilation at any time during 28 days post baseline
8. Use of mechanical ventilation / ECMO at any time during 28 days post baseline
9. Acute renal injury/acute renal failure at any time during 28 days post baseline
10. Liver dysfunction at any time during 28 days post baseline

Note: length of hospital stay was a key outcome of the SOLIDARITY trial, but is not listed as an outcome here. This is because our cohort includes hospital acquired COVID patients, and some patients with long-term institutionalisation. We are more interested in COVID-related hospital stay, but data on this are not collected beyond 28 days, and so we use the outcome 'Time-to-recovery' to double as inference to test whether RDV impacts on short-term length of stay.

10. Sample size

This is a prospective observational study of RDV made at the request of the Chief Medical Officer of Her Majesty's Government. As such there is no formal sample size calculation. We expect a sufficiently large sample size (n>500 patients treated with RDV satisfying inclusion criteria) to allow meaningful analysis, but there will be no upper boundary placed on the numbers included (data are routinely

e This is an outcome defined in the ACTT-1 trial.

collected as part of a wider study). The number of controls cannot be predicted – the ratio of RDV to controls will be at least 1:1, but could be as high as 1:4.

11. Study Framework

This is a prospective observational study of RDV. It's objective is to evaluate RDV in the context of its use initially under EAMS and then under standard guidelines in the UK. Hypotheses will test for superiority. Outcomes are defined to allow direct comparisons with the clinical trial outcomes defined in ACTT-1 and SOLIDARITY. The scope of this study to measure isolated efficacy of RDV is clearly limited by the observational nature of the data; but the evaluation of outcomes will give a pragmatic summary of the current prognosis for this population of severe COVID with and without RDV.

12. Confidence Intervals, p-values and Multiplicity

Confidence intervals will be reported for all point estimates at the 95% level. Baseline summaries will be presented to 1 decimal place whilst all other values will be reported to 2 decimal places, or 1 significant figure if it would round to zero at 2 decimal places, and all p-values will be reported to 3 decimal places. There are no planned adjustments for multiplicity.

13. Timing and objectives of interim and final analyses

13.1. Progress reports

No interim/progress reports are planned. At the time of writing, RDV is no longer the subject of an EAMS objective, and the study's aim is simply to evaluate its use thus far.

13.2. Final analysis

Data collection will continue until the end of November 2020, in order to include patients from both the 1st and 2nd wave of UK COVID infections. It is then envisaged that the statistical analysis will be completed by the end of January 2021.

14. Disposition of Participants

A CONSORT style flow-chart will summarise the flow of patients through analysis stages: the number of patients with an admission CRF recorded by CCP-UK; the number of patients included and excluded due to inclusion/exclusion criteria; of those included – the numbers that received RDV; numbers of non-RDV patients; the total number of RDV and non-RDV patients included in the matched analysis; numbers of RDV patients and matched controls included in the primary outcome analysis.

15. Treatments received

This study did not define an *a priori* protocol for clinicians treating COVID-19 patients. Reporting of protocol deviations will be limited to a count of patients that did not receive RDV according to guidelines, and to an assessment of missingness in the derivation of the primary and secondary outcomes. Treatments received are recorded in the Medication section of the Outcome CRF. These will be summarised in the matched cohort, split by treatment group. If there is evidence of imbalance between groups with respect to certain treatments, we will consider whether to adjust for this in the final analysis.

16. Unblinding

Not applicable.

17. Efficacy Evaluations

17.1. Demographics and other baseline characteristics

Descriptive statistics will be used to describe demographics and other baseline characteristics, including pre-existing comorbidities for (a) the full analysis cohort, (b) the matched cohort, split by treatment group.

Categorical data will be summarised by numbers and percentages. Counts for missing values will be also tabulated but missing values will not be considered in the percentages. Continuous data will be summarised by mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum. Variables to be included are as follows:

- Gender (Male/Female)
- Age, reported as a continuous variable (years) and also by age-group (18-30,…,71-80, 81+)
- Broad ethnicity (White / Black / Asian / Other)

- Non-white ethnic origins (Arab/Black/East Asian/South Asian/West Asian/Latin American/Aboriginal/First Nations/Other)
- Clinically extremely vulnerable status (None / Cancer / Severe respiratory condition / Immunosuppression therapy / Other)
- Comorbidities (Diabetes, Hypertension, Obesity, Chronic Cardiac disease, CPD, Asthma, Other)
- Where COVID was acquired (Community / Hospital)
- Number of days since onset of symptoms
- Admitted to HDU/ICU

17.2. Analysis of Outcomes

17.2.1. Primary Outcome

The percentage of patients that died by the end of day 14 will be presented for each group. Risk of death will be modelled using logistic regression[f,10], with treatment group fitted as a covariate, and ideally adjusting for the key confounders: age, sex, and number of comorbidities at baseline. The odds-ratio comparing RDV with controls, estimated from the model, will be presented together with a 95% CI and a p-value.

Note on adjustment for confounders: the number of covariates that may be added to the model depends on the number of deaths recorded (rule of thumb, 10 events per covariate fitted). Clinical trials data indicate that 14-day mortality for RDV in this type of patient may be around 3.1%, meaning that if we include 500 RDV-treated patients, we might expect 16 deaths from that group. Under the assumption that the risk of death is not lower in the control group, this suggests at least 32 deaths (under 1:1 matching), and so we project that there will be sufficient power to enable adjustment for 3 confounders given the higher expected matching ratio.

f Stuart (2010) recommends that in the analysis of cohorts matched using propensity scoring, it is more common to simply pool all the matches into matched treated and control groups and run analyses using the groups as a whole, rather than using the individual matched pairs.

17.2.2. Secondary Outcomes

17.2.2.1. Time to recovery

Recovery is defined as discharge from hospital or continued hospitalisation with no on-going health-care needs related to COVID-19. For patients that recover, a time-to-event is defined as the number of days from baseline to discharge, or from baseline to cessation of COVID-19 related health-care (whichever occurs first). All other patients are censored at last available follow-up or 28 days (whichever occurs first). All deaths before 28 days (with no prior recovery) will be censored at day 28[g]. A Cox proportional hazards model will be used to model time-to-recovery, fitting treatment as a covariate, and adjusting for the key confounders: age, sex, and number of comorbidities at baseline. The hazard ratio comparing RDV with controls estimated from the model will be presented together with a 95% CI and a p-value. Kaplan-Meier graphs comparing recovery by treatment group will be presented – for the full matched cohort; and for key age-groups: <50, 50-59, 60-69, 70-79, ≥80 years.

17.2.2.2. 28-day mortality

The same methodology as used in 17.2.1 above will be applied here for risk of death at day 28.

17.2.2.3. Time-to-death

We restrict this analysis to deaths within 28 days of baseline. Any patient alive at the end of the study period will be censored at 28 days. Any patient lost to follow-up prior to 28 days will be censored at their last known follow-up. This outcome will be analysed as a time-to-event using the methodology described in 17.2.2.1 above.

17.2.2.4. Clinical status at day 15

Clinical status is defined as an 8-point ordinal score with the following categories: (1) Not hospitalised, and not limited physically; (2) Not hospitalised, but limited physically and/or requiring supplementary oxygen; (3) Hospitalised but medically OK; (4) Hospitalised, not requiring supplementary oxygen, but needs on-going COVID related care; (5) Hospitalised and requiring supplementary oxygen; (6) Hospitalised and requiring non-invasive ventilation; (7) Hospitalised and requiring mechanical ventilation or ECMO; (8) Dead. See Appendix A1.1 below for a definition of how this outcome is derived. Where day 15 CRFs are unavailable, we will look at all available adjacent CRFs to estimate a

g We have used the same definition for this outcome as was used in the ACTT-1 trial.

most likely clinical status. In cases where there is ambiguity over likely clinical status, and independent statistical reviewer, blind to all but the clinical status CRF data, will adjudicate likely status. If it is not possible to estimate the outcome, the outcome will be treated as missing.

The outcome will be analysed using a proportional odds model with treatment arm and disease severity as covariates, and adjusting for key confounders: age, sex, and number of comorbidities at baseline. The treatment odds ratio estimated from the model will be presented along with a 95% CI and a p-value.

17.2.2.5. Length of time receiving supplementary oxygen

The DAILY CRF will be used to determine the number of days where oxygen was recorded as given. Missing daily CRFs will be imputed if and only if adjacent days are not missing, and as follows:

Day before	**Day after**	**Impute for missing day**
Oxygen	Oxygen	Oxygen
No oxygen	No oxygen	No oxygen
Oxygen	No oxygen	0.5 days on oxygen
No oxygen	Oxygen	0.5 days on oxygen

The outcome will be the total number of days either known or imputed to be on oxygen. Days where no imputation is possible will be excluded from the analysis, under the assumption that missingness is equally likely regardless of treatment. An assessment of the proportion of missing daily CRFs per patient will be made for each treatment group to check this assumption: an arbitrary margin of acceptability of an absolute difference of 10% will indicate the assumption holds. If the assumption holds, 'Days on oxygen' will be modelled using linear regression, with treatment group fitted as a covariate, and adjusting for the key confounders: age, sex, and number of comorbidities at baseline. The mean (SD) days will be presented for each treatment group, and the difference in days comparing RDV with controls, estimated from the model, will be presented together with a 95% CI.

If the assumption does not hold, modelling will not be used, and only descriptive statistics will be presented.

17.2.2.6. Time-to-first ventilation

The DAILY CRF will be used to define, where possible, date of first use of ventilation. Any patient not recorded as ventilated that is lost to follow-up or dies before 28 days, will be censored at the date of last follow-up, or date of death. This outcome will be analysed as a time-to-event using the methodology described in 17.2.2.1 above.

17.2.2.7. Use of non-invasive ventilation at any time during 28 days post baseline

The total number of patients requiring any non-invasive ventilation during the 28 days post baseline will be presented. The effect of RDV on the risk of requiring non-invasive ventilation will be evaluated using the same methodology as used in 17.2.1 above.

17.2.2.8. Use of mechanical ventilation / ECMO at any time during 28 days post baseline

The total number of patients requiring any mechanical ventilation/ECMO during the 28 days post baseline will be presented. The effect of RDV on the risk of requiring mechanical ventilation/ECMO will be evaluated using the same methodology as used in 17.2.1 above.

17.2.2.9. Acute renal injury/acute renal failure at any time during 28 days post baseline

The total number of patients experiencing either acute renal injury or acute renal injury during the 28 days post baseline will be presented. The effect of RDV on the risk of this complication will be evaluated using the same methodology as used in 17.2.1 above.

17.2.2.10. Liver dysfunction at any time during 28 days post baseline

The total number of patients experiencing any liver dysfunction during the 28 days post baseline will be presented. The effect of RDV on the risk of this complication will be evaluated using the same methodology as used in 17.2.1 above.

18. Missing data and Withdrawals

It is anticipated that there will be a degree of missing data, and that some outcomes may not be accurately measurable for all patients. A key impact of missingness will be in the matching process – a propensity score is only calculable for patients with complete data with respect to matching variables. If sample sizes are significantly reduced, it may be necessary to reduce the number of matching variables. If there is a large amount of missing comorbidity data, we will consider changing measures from individual comorbidities, to a measure of 'number of comorbidities ticked'. All decisions on missing data handling will be documented, but cannot easily be predefined prior to seeing the data.

In the case of missing time-to-event data, censoring will be used so that at least some data may be included.

Accounting for types of missingness – missing at random, missing completely at random, and missing systematically is beyond the scope of the analysis.

Any patient that withdraws permission for their data to be analysed will be excluded from all analyses.

19. Additional analyses

The analyses described above will be reproduced for the subgroup of patients that were ventilated during the 1st 24 hours post baseline. The sample size is expected to be small, so analyses may be simplified and/or restricted to descriptive statistics.

20. Safety

The number and percentage of patients experiencing specific complications at any time during the 28 days post baseline, will be reported for both groups. Complications to be summarised are those appearing on the Outcome CRF.

21. Declarations

The manufacturer of Remdesivir, Gilead, is also involved in funding other trials that the Liverpool Clinical Trials unit is co-ordinating: a randomised controlled trial (HART-CT) that is fully funded by Gilead and sponsored by the University of Liverpool; and a trial (REALTO) that is part funded by Gilead. Dr Jones is the lead statistician on the HART-CT trial.

22. References

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Appendix

Table 1: Clinical status ordinal score at day 15 mapped to ISARIC data fields

Score	Clinical Status	ISARIC v9.3 Data Field(s)
1	Not hospitalised, and no limitations on activities	**OUTCOME CRF (if dated day 15 or less):** • Discharged alive expected to survive = YES AND • Ability to self-care at discharge = 'Same as before illness' OR 'Better' AND • Oxygen therapy?* = NO OR • Hospitalisation= YES AND • Medically fit for discharge = YES
2	Not hospitalised, limitation on activities and/or requiring home oxygen	**OUTCOME CRF (if dated day 15 or less):** • Discharged alive expected to survive = YES AND • Ability to self-care at discharge = 'Worse' OR • Oxygen therapy? = YES
3	Hospitalised, not requiring supplemental oxygen – no longer requiring ongoing COVID related medical care	**OUTCOME CRF (dated day 15 or less):** • Hospitalisation= YES AND • Ongoing health care needs NOT related to COVID = 'YES'
4	Hospitalised, not requiring supplemental oxygen, requiring on-going COVID related care	**DAILY TREATMENT CRF (day 15):** • Any supplemental oxygen = NO • Non-invasive respiratory support = NO • Invasive respiratory support = NO • Non-invasive ventilation = NO • High-flow nasal cannula = NO • ECMO = NO
5	Hospitalised, requiring supplemental oxygen	**DAILY TREATMENT CRF (day 15):** • Any supplemental oxygen = YES • Non-invasive respiratory support = NO • Invasive respiratory support = NO • High-flow nasal cannula = NO • ECMO = NO
6	Hospitalised, on non-invasive ventilation or high flow oxygen devices	**DAILY TREATMENT CRF (day 15):** • Non-invasive respiratory support = YES OR • High-flow nasal cannula = YES AND • Invasive respiratory support = NO • ECMO = NO OR • FiO2 >0.4, or FiO2 >40%

		OR • O2 flow > 4 L/min
7	Hospitalised, on mechanical ventilation or ECMO	**DAILY TREATMENT CRF (day 15):** • Invasive respiratory support =YES OR • ECMO = YES
8	Death	**OUTCOME CRF (dated day 15 or less):** • Death= YES
NA	Unable to classify	If death before day 15, lost to follow-up prior to day 15, or due to incomplete CRF completion

* If use of supplemental oxygen is unknown or missing, use either (1) DAILY CRF: recorded "Oxygen saturation" SpO2 lowest % is ≥94%; or (2) DAILY CRF: recorded "Oxygen saturation" SpO2 lowest % is ≥88% plus: Admission CRF co-morbidities "Chronic pulmonary disease" is "Yes".