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ABSTRACT:

Background: COVID-19 is associated with significant morbidity and mortality. This study aims to synthesise evidence to assess the cost-effectiveness of remdesivir (RDV) for the treatment of hospitalised patients with COVID-19 in England and Wales.

Methods: A probabilistic cost-effectiveness analysis was conducted informed by two large trials and uses a partitioned survival approach to assess short and long-term clinical consequences and costs associated with COVID-19 in a hypothetical cohort of hospitalised patients requiring supplemental oxygen at the start of treatment. As it is uncertain whether RDV reduces death, two analyses are presented, assuming RDV either reduces death or does not. Published sources were used for long-term clinical, quality of life and cost parameters.

Findings: Under the assumption that RDV reduces death, the incremental cost-effectiveness ratio (ICER) for RDV is estimated at £11,881 per QALY gained compared with standard of care (probabilistic ICER: £12,400). The probability for RDV to be cost-effective is 74% at a willingness to pay threshold of £20,000 per QALY gained. RDV was no longer cost-effective when the hazard ratio for overall survival compared with SoC was greater than 0·915.

Interpretation: Results from this study suggest that using RDV for the treatment of hospitalised patients with COVID-19 is likely to represent a cost-effective use of National Health Service resources at current WTP threshold in England and Wales, only if it prevents death. Results needs to be interpreted caution as vaccination was introduced and the standard of care and evidence available has also evolved considerably since the analysis is conducted.

Introduction

COVID-19 is caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and causes atypical pneumonia.[1] The disease is transmitted by inhalation or contact with infected droplets and the incubation period is estimated to range from two to 14 days.[2] The symptoms are usually fever, cough, breathlessness, and fatigue, amongst others.[2] All populations are susceptible to SARS-CoV-2, with the elderly and people with underlying diseases or low immune function being more likely to become severe cases.[1]

In response to the public health emergency, NHS England issued an interim commissioning policy (first published on the 7th July 2020 and updated on the 12th November 2020) for the use of remdesivir (RDV) in England and Wales,[3] for the treatment of hospitalised patients with COVID-19 requiring supplemental oxygen at the start of treatment (as per its European Medicines Agency [EMA] marketing authorisation[4]), typically defined as those on low-flow oxygen (LFO), high-flow oxygen (HFO) or other non-invasive ventilation (NIV).

The efficacy of RDV in hospitalised patients with COVID-19 on supplemental oxygen is described in a number of studies that are heterogeneous in terms of the included populations, study design and outcomes. ACTT-1[5] is a double-blind randomised controlled trial (RCT) comparing RDV against placebo in the US and reported a treatment effect on mortality (hazard ratio (HR)) of 0·30 (95% confidence interval [CI] 0·14–0·64) in hospitalised patients with LFO and 1·02 (95% CI 0·54–1·91) in patients with HFO or NIV at baseline. SOLIDARITY[6] was conducted following ACTT-1 and is an unblinded, multicentre RCT across 30 countries in patients who were hospitalised with COVID-19. ACTT-1 compared RDV to local standard of care and reported a rate ratio of death of 0·85 (95% CI 0·66–1·09) for the subgroup of patients requiring any supplemental oxygen (but not mechanically ventilated). Wang et al (2020),[7] was conducted in China and compared RDV against placebo in a double-blind RCT and reported a death rate ratio of 0·81 (95% CI 0·21–3·07) in hospitalised patients with LFO and 1·40 (95% CI 0·20–9·52) in patients with HFO or NIV at baseline. There is therefore considerable uncertainty in the effectiveness of RDV in preventing death in the overall supplemental oxygen population. These RCTs were also conducted at different phases during the pandemic making any direct comparison challenging.

NHS England's interim commissioning for RDV[3] was produced in response to the public health emergency and the rapid need for effective treatments to help reduce morbidity and mortality posed by COVID-19. This decision was not based on economic consideration. It is therefore unclear whether RDV represents a cost-effective use of NHS resources in England and Wales for the treatment of hospitalised patients with COVID-19 on supplemental oxygen at entry.

The objective of this study is to assess the cost-effectiveness of RDV in England and Wales within its current marketing authorisation[4] and interim NHS commissioning policy, from a health services perspective.[3]

Strategies compared and population entering the model

A decision-analytical model was constructed in Microsoft Excel to assess the short-term (during the hospitalisation episode) and long-term (following hospital discharge) clinical consequences and costs associated with COVID-19 in a hypothetical cohort of hospitalised patients requiring supplemental oxygen at the start of treatment (defined as patients on LFO or HFO or NIV) in England and Wales.

The intervention assessed is RDV (Veklury®) 200mg on day one, followed by RDV 100mg maintenance up to five days, in line with current NHS England interim commissioning for RDV.[3] The comparator is established clinical management (prior routine use of tocilizumab [TCZ] and sarilumab [SAR]) with or without corticosteroids. RDV is assessed as an adjunct to standard of care.

Model structure

The structure of the decision-analytical model is depicted in Fig 1. and uses what is commonly referred to as a partitioned survival/area under the curve (AUC) approach, composed of three main mutually exclusive health states; (i) discharged from hospital and alive, (ii) hospitalised with or without COVID-19 and (iii) death from any cause (COVID-19 or due to other causes).

[INSERT FIGURE 1 HERE]

Patients enter the model when hospitalised with COVID-19 and requiring supplemental oxygen (LFO, HFO or NIV) at the start of treatment. During their hospital stay (defined as the AUC between the time to death and discharge curves), patients are further separated into five hospitalisation sub-health states based on their hospitalisation/oxygen requirement according to the clinical status ordinal scale as defined in the ACTT-1 trial[5] (i.e. no care due to COVID-19, ii. No oxygen, iii. LFO, iv. HFO or NIV and v. invasive ventilation), each associated with different cost and utility impact. Movements between hospitalisation health states are not explicitly modelled. Instead, the partitioned model deals with health state occupancy within each time intervals.

Due to their short duration, not everyone in trials for COVID-19 treatments will have been discharged or died at the time of outcome assessment. Therefore, time to death is extrapolated parametrically beyond the trial duration using a daily cycle length up to 70 days (35 days in the base-case), followed (weekly cycle length) by an elevated risk of death[8] compared with background mortality up to week 52

(varied between 6 months to 2 years in sensitivity analysis), and unadjusted background mortality used thereafter.Time to discharge is extrapolated parametrically until everyone either dies or is discharged.

Discharged patients are assumed to have a reduced quality of life (52 weeks from model entry in the base-case) to reflect emerging evidence on the effect of COVID-19 following hospital discharge.[9-11] Emerging evidence also suggests that some patients are at an elevated risk of multi-organ dysfunctions[8] (such as respiratory diseases, diabetes, cardiovascular, liver and kidney diseases) and may require long term management/monitoring.[12] These potential impacts are included in this economic model as an average one-off cost and QALY loss per patient discharged.

Model parameters

Baseline characteristics

The mean age and gender distribution at entry (Table 1) are taken from a UK study amongst 47,780 hospitalised patients with COVID-19 and discharged alive.[8]

Time to death in patients initiated on SoC (prior use of RDV)

The time to death in patients for the SoC arm is taken from a large UK trial; the first RECOVERY trial that compared usual care vs. corticosteroids (dexamethasone).[13] Since this trial was conducted, clinical practice has changed with corticosteroids widely used. Therefore, a weighted spline model (three knots) was constructed from the pseudo-IPD (reconstructed based on a published algorithm[14]) that assumes that 90% of patients are on corticosteroids (dexamethasone arm from RECOVERY[13]), with the remaining not on dexamethasone (usual SoC from RECOVERY[13]). A spline model with three knots was selected following visual inspection and statistical tests; with the addition or removal of knots not materially changing the fit within the observed or short-term extrapolation in this study. Scenario analyses are conducted using the control arm from SOLIDARITY[6] or the control arm from the RECOVERY TCZ trial[15] in people with progressive COVID-19.

Time to discharge in patients initiated on SoC (prior use of RDV)

The time to discharge for the SoC arm is approximated by adjusting a spline model (three knots) estimated from pseudo-IPD from the control arm from SOLIDARITY[6] using an HR we calculated so that the proportion of patients predicted to be discharged and alive at day 28 matches the proportion reported in the RECOVERY trial[13] (70·86% for the weighted analysis [base-case: 90% assumed to

receive corticosteroids], 67·40% [n=1,755/2,604] for usual care without dexamethasone, 72·01% [n=921/1,279] for the dexamethasone arm).

Treatment effects for RDV

The effectiveness of RDV at reducing death in patients on supplemental oxygen at entry is very uncertain and therefore two analyses are conducted. The base-case uses the point estimate from the on-oxygen population subgroup from SOLIDARITY[6] (Ratio of death rate: 0·85; 95% CI 0·66–1·09). A secondary analysis is presented assuming an HR of 1 (e.g. RDV does not have an impact on survival) as the treatment effect is not statistically significant despite the large sample size for this subgroup in SOLIDARITY (n=3,639).[6] Similar findings were observed in Wang et al (2020).[7] A significant treatment effect was also reported in patients with LFO in ACTT-1, but not in HFO.[5]

The treatment effects for time to discharge are estimated from the published data (IPD reconstructed using a published algorithm[14]) from SOLIDARITY[6] using piecewise HRs (day 0-4, 5-9, 10-14, 15-19, 20+) calculated simultaneously in a model that is stratified by time group.

Distribution of patients by intensity of hospital care required

The distribution of hospital care type in patients initiated on RDV is shown in Fig 2. The distribution at baseline and at day 14 are informed by the distribution (derived from the ordinal scale of clinical status) from the ACTT-1 trial[5] and Goldman et al[16] (RDV for five and ten days). We then assumed that the proportion of patients on invasive ventilation, NIV and no longer on oxygen increased linearly from day 0 to 14 and was carried forward beyond day 14 informed by the trend observed in ACTT-1 for RDV.[5]

[INSERT FIGURE 2 HERE]

The treatment effect for the probability of ventilation in patients initiated on SoC (compared with RDV) is taken from an unpublished UK study[17] for the base-case, and assumed to be same as RDV for the secondary analysis assuming no survival difference.

Mortality rate beyond parametric extrapolation

The unadjusted rate of mortality for the general population is taken from the England and Wales life table 2017-2019.[18] Between the end of extrapolation (day 35 in the base-case) and week 52, patients hospitalised with COVID-19 are assumed to be, on average, at an elevated risk of death of 7·7 (95% CI 7·2–8·3) compared with the general population based on the rate ratio reported by Ayoubkhani et al (2021) in the UK.[8]

Costs

We adopt a health service perspective. Unit costs are summarised in Table 1. The unit costs per hospital bed day, according to the intensity of care required as measured by the ordinal scale of severity, are taken from NHS reference costs.[19] The list price for RDV is taken from the BNF.[20] The number of RDV doses is taken from an unpublished UK study.[17]

Only drug costs for corticosteroids are included for SoC and calculated from the electronic market information tool (eMIT)[21] based on the weighted average of relevant formulations.

As the population entering the model is hospitalised, additional administration costs are likely to be minimal and are therefore not included in this economic evaluation.

[INSERT TABLE 1 HERE]

Health utilities

Health utility values are summarised in Table 1. Utility values are age-adjusted as patients get older based on Ara et al (2010), with the baseline utility value pre-COVID-19 estimated from the mean age at entry, adjusted by a decrement in utility taken from Ara et al[22] to reflect increased comorbidities for patients with COVID-19 compared with the general population.[8, 23] During the hospitalisation episode, decrements in utility values are applied (subtracted) to the baseline, taken from the published literature.[24, 25] As with the assignment of costs, these utility decrements align with the degree of care required whilst in hospital as indicated by the ordinal scale. Following hospital discharge patients with COVID-19 have a reduced quality of life,[8] with quality of life returning to pre-COVID-19 baseline after 52 weeks.

Increased risks of multi-organ dysfunction and monitoring – One off cost and QALY decrement at the point of discharge

A one-off cost and QALY loss per patient discharged (Table 1) is applied in the economic model to reflect the elevated risk of multi-organ dysfunction after COVID-19 hospitalisation (assumed to last a

year). These are calculated from the rates reported by Ayoubkhani et al (2021) in the UK[8] in patients hospitalised with COVID-19 compared with matched-controls and assumptions on costs and QALY loss (Supplementary Table 1).

Increased monitoring/follow-up is assumed to occur in the first year only. An average one-off cost (Table 1) is applied at the point of discharge calculated based on the assumption that discharged patients require on average two chest X-ray and six GP e-consultations, and unit costs from Stroke et al (2016)[26] and PSSRU (2020).[27]

Analysis

In accordance with the NICE reference case,[28] patients are followed over a lifetime horizon, an NHS/PSS perspective is used and costs and benefits are discounted at 3·5% per annum.

Results are presented both deterministically and probabilistically to take account of the simultaneous effect of uncertainty relating to model parameter values. A total number of 1,000 simulations were performed in order to obtain sufficient precision. Base-case results are also presented as cost-effectiveness (CE) planes and cost-effectiveness acceptability curves (CEAC).

The treatment effect for RDV on OS is a key driver and highly uncertain. Consequently, a threshold analysis is conducted, with results presented in terms of net monetary benefits (NMB) to determine the point at which RDV is no longer cost-effective at a WTP of £20,000 under our base-case assumptions. Threshold analysis to determine the cost-effective price was also conducted. A range of sensitivity and scenario analyses are also conducted to test the robustness of results to key input parameters/assumptions (Supplementary Table 2).

Results

Base-case analysis: assumption that RDV reduces death – using the point estimate for the treatment effect observed in on-oxygen subgroup of SOLIDARITY

Table 1 presents the deterministic and probabilistic results. For the probabilistic analysis, under the assumption that RDV reduces death, the model estimates total discounted costs associated with RDV to be £12,758 compared with £9,393 for established clinical management, an incremental cost of £3,365. The total discounted QALYs for RDV are estimated to be 6·62 compared with 6·35 for patients treated with established clinical management, an incremental QALY gain of 0·27. The probabilistic ICER is £12,400 per QALY gained.

[INSERT TABLE 2 HERE]

We found that 89·3% of monte-carlo simulations comparing RDV versus established clinical management were in the northeast quadrant (more costly and more effective) of the cost-effectiveness plane. RDV was more costly but less effective in 10·7% of case (northwest quadrant – Figure 3). Cost-effectiveness acceptability curves demonstrate that RDV has a 74% probability of being a cost-effective treatment option at a £20,000/QALY gained willingness-to-pay (WTP) threshold.

[INSERT FIGURE 3 HERE]

Secondary analysis: RDV does not reduce death

When it is assumed that RDV does not reduce death, RDV is predicted to lead a very small increase in QALYs (0·00002), at an incremental cost of £1,666, leading to a high ICER (over £1 million/QALY). Approximately half (52·2%) of monte-carlo simulations were in the northeast quadrant (more costly and more effective) of the cost-effectiveness plane, with RDV having a 0% probability of being a cost-effective treatment option at a £20,000/QALY gained WTP threshold.

Threshold analyses

At its current list price, the threshold analysis (Figure 3) shows that RDV is no longer cost-effective at a WTP of £20,000 per QALY gained when the HR is greater than 0·915.

[INSERT FIGURE 4 HERE]

If no survival difference is assumed between RDV and SoC, the price per 100 mg vial for RDV needs to be less than £18·6 for RDV to be cost-effective under current WTP threshold.

Scenario analyses

In addition to the treatment effect for OS and list price for RDV, ICERs were affected the most by the model time horizon, the baseline curve for SoC (patients with progressive COVID-19 included in the RECOVERY TCZ trial) and inclusion of unrelated costs.

Discussion

This is the first study to undertake an economic evaluation of the use of RDV for the treatment of hospitalised patients with COVID-19 in England and Wales. This study found that, whilst RDV reduces time to recovery, it is likely to be cost-effective only if it also prevents death. However, the effectiveness of RDV at reducing death is highly uncertain within the overall supplemental oxygen population. Evidence suggests that patients requiring LFO are more likely to derive benefits from RDV compared with patients on HFO or NIV. RDV is therefore likely to represent a cost-effective use of NHS resources in patients with LFO only. The analysis was conducted during the second wave of the pandemic. Since the analysis was conducted, vaccination was introduced in the UK and the standard of care and evidence available for RDV has evolved considerably. Results from this analysis should therefore be interpreted in this context.

This study also sets out a framework to capture the key drivers of costs and benefits (mortality, duration of stay and intensity of care required while in hospital) that can be used to rapidly evaluate other treatments for hospitalised patients with COVID-19. This is important during a public health emergency as COVID-19 is associated with significant morbidity and mortality and therefore there is need to inform public policy rapidly and ensure that NHS resources are allocated efficiently and fairly.

A key strength of this study is that it addresses an important public health question for decision makers in the light of uncertain information, synthesises many sources and reflects uncertainty. This emphasizes the value of modelling given the difficulty to conduct clinical research in a rapidly changing environment. Key strengths of this study also include that it is based on two large open-label trials; the RECOVERY trial[13] and SOLIDARITY.[6] This study also focuses on patients treated with RDV on supplemental oxygen at the start of treatment (defined as LFO, HFO or NIV) in line with its European marketing authorisation and NHS England commissioning policy.[3, 4] The duration of hospitalisation is calculated from the area under the curve of OS and time to discharge curves with outcomes extrapolated beyond the trial duration to account for the fact that a proportion of patients are neither dead, nor discharged by day 28 in the respective trials. Albeit with some simplification due to limitations with the evidence base, this economic evaluation attempts to include some of the short, medium and long-term effects associated with COVID-19 (elevated risk of death, reduced quality of life, elevated risk of multi-organ dysfunctions and increased monitoring) alongside movement between the different hospitalisation oxygen requirements (with costs and QALYs calculated accordingly). Uncertainty in the model inputs and assumptions has also been explored extensively in a number of scenario and sensitivity analyses.

Results are not directly comparable to other published economic evaluation for RDV[29-31] as there are a number of important differences in terms of population considered, comparators, methodology and

evidence used. Previous published economic evaluations[29-31] at the time this analysis was conducted employed a decision-tree approach with patients considered either recovered or dead during the first month, followed by a Markov model or pay off. The population included in previous economic evaluations[29-31] was also broader including patients not on oxygen at or on invasive ventilation at the start of treatment. This differs from the licensed indication for remdesivir in Europe which specifies patients with pneumonia requiring supplemental oxygen. The duration of hospitalisation is also calculated differently, derived from the OS and time to discharge extrapolated curves in our model compared with a more simplistic approach in previous economic evaluation based on the median time to recovery in recovered patients and assumptions for those died.[29] In our model, hospitalised patients are also able to move (implicitly) between different hospitalisation/oxygen requirements with costs and QALYs calculated accordingly. In Campbell et al (2020) for instance, hospitalisation costs are calculated based on the oxygen support required as highest level of respiratory support (one off cost not based on duration of hospitalisation) and are disconnected from the starting health state, and therefore only applicable for the overall ACTT-1 population.[29] Compared with previous economic evaluations,[29-31] our model further considers that COVID-19 patients are, on average, at an elevated risk of death, reduced quality of life and multi-organ dysfunctions following discharge. None of these effects were included in previous published economic evaluations at the time this analysis was conducted.[29-31]

As with any economic evaluation, there are limitations to be acknowledged. First, any economic evaluation for COVID-19 is challenging to conduct due to the rapidly changing environment. Standard of care is consistently evolving and has changed since the evidence used in this economic evaluation was published. Corticosteroids are now the SoC in England and Wales and this has been reflected in the base-case. NHS England recently issued advise for the use of tocilizumab and sarilumab. Unlike RDV, tocilizumab and sarilumab have different mechanisms of action and it is unclear to what to extent these treatments would be considered in patients that would have been otherwise eligible for RDV in England and Wales (and be appropriate comparators). Albeit limited to the supplemental oxygen subgroup from the respective source of evidence, this economic evaluation combine evidence from different studies that are heterogeneous in population, design and outcomes. The level of patients' oxygen requirement was also not reported.

Evidence is also constantly evolving. For instance, time to discharge had to be approximated as only the proportion of events at the end of trial was reported at the time of conducting study, but new data have now been published. Using the recently published KM was explored (Supplementary Table 2). The model therefore needs to develop as more evidence is available on both the impact of treatments on COVID-19 and its long-term effect. Since this analysis was conducted, additional evidence of the effectiveness RDV has been published from a phase 3, open-label, adaptive, multicentre, randomised, controlled trial conducted in 48 sites in Europe (DisCoVeRy).[32] This study found that no clinical

benefit was observed from the use of remdesivir in patients who were admitted to hospital for COVID-19 and requiring oxygen support.

The model uses an area under the curve approach which does not allow us to track individual patients, leading to assumptions being required. A cohort partitioned survival approach was chosen in the absence of individual patient level data from the key relevant trials/studies used in this economic evaluation and necessity to work with aggregate published data. This is a limitation as patients with COVID-19 admitted to the hospital are heterogeneous, with important factors impacting the progression of their disease. It was also not possible to conduct subgroup analysis in the absence of subgroup data reported in patients on supplemental oxygen at entry. Treatment effects from studies evaluating RDV for ten days are used as a proxy for RDV for five days. The assumption of equivalence for survival is likely to be reasonable and is supported by Goldman et al (2020) and Spinner et al (2020), albeit in a broader population. The trend for time to discharge is taken from SOLIDARITY where patients were treated up for to 10 days, which could have affected the decision to discharge patients. It is possible that patients on RDV in SOLIDARITY were kept longer at the hospital to finish the ten-day course.

Analyses are conducted at list prices. Any confidential discount offered to the NHS is not considered in this analysis. It is also unclear whether RDV reduces or increases ventilation/oxygen support due to mixed evidence.

Since this economic evaluation was conducted, two UK studies; the PHOSP-COVID collaborative group[10] and ISARIC[11] reported estimates on quality of life pre-COVID-19 and for lower mean age. It is therefore unclear whether the additional decrement in utility associated with comorbidities included in this analysis was required and led to double counting. This was explored in a scenario analysis and led to an improvement in the ICER (Supplementary Table 2).

Assumptions were required to capture the effect of COVID-19 in the medium to long-term. It is unclear how long discharged COVID-19 patients are at an elevated risk of death or reduced quality of life. It is also unclear whether multi-organ dysfunctions reported in the literature are acute (temporary) or chronic. The approach to capture costs and impact on quality of life associated with multi-organ dysfunction is simplistic due to the heterogeneity in patients experience and doesn't take into account patients with post-COVID 19 Syndrome and the recommendation for them to have rehabilitation. It also does not take account of other reported long-term effects on mental health that have been reported such as post-traumatic stress disorder. The duration and frequency of monitoring following discharge of patients with COVID-19 is also unknown and challenging to capture due to the heterogeneity in patient experience. The mortality, costs and morbidity impact associated with re-admission due to COVID-19 is not included separately to avoid double-counting as evidence suggests that re-admission due to COVID-19 occurs shortly following the initial hospitalisation episode, typically within five to ten days.[5, 33]

The model conservatively assumes that patients initiated on RDV or standard of care experience the same long-term outcomes, in the absence of evidence. Consequently, any short-term difference in survival, will translate into commensurate gain in the long-term. It is possible that outcomes for patients initiated on RDV may be worse if more patients require ventilation due to the reduced death rate.

Conclusion

RDV is likely to represent a cost-effective use of NHS resources if it reduces death and does not increase ventilation requirement. RDV is likely to be more cost-effective in patients requiring LFO at entry only compared to those requiring more intensive HFO or NIV.

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Figure 1: Model structure

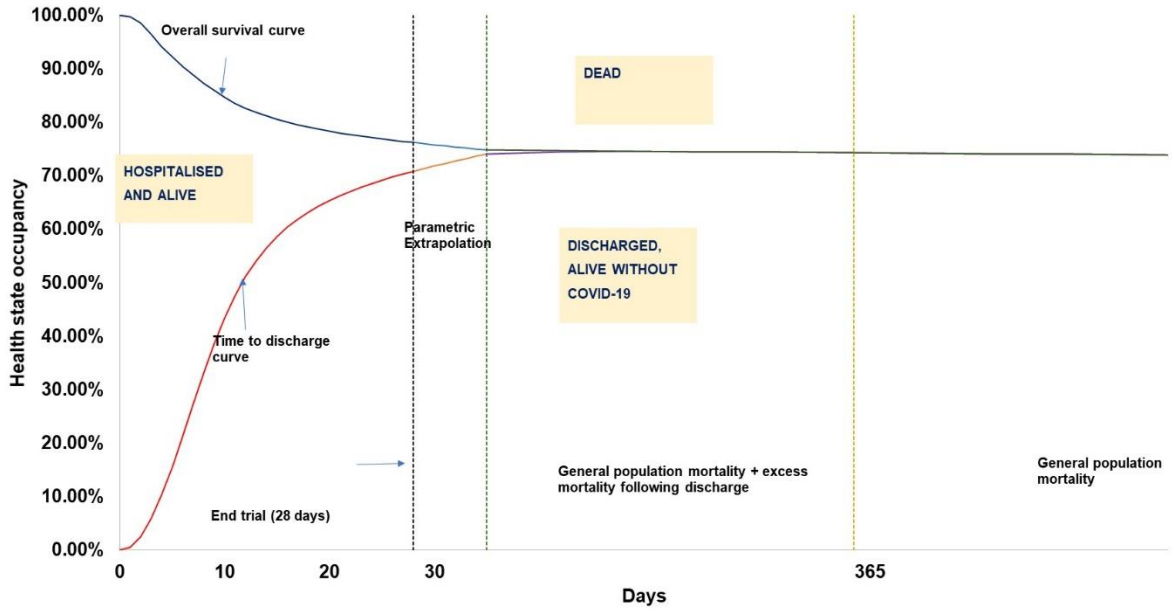


Figure 2: Hospital health state occupancy in patients initiated on RDV

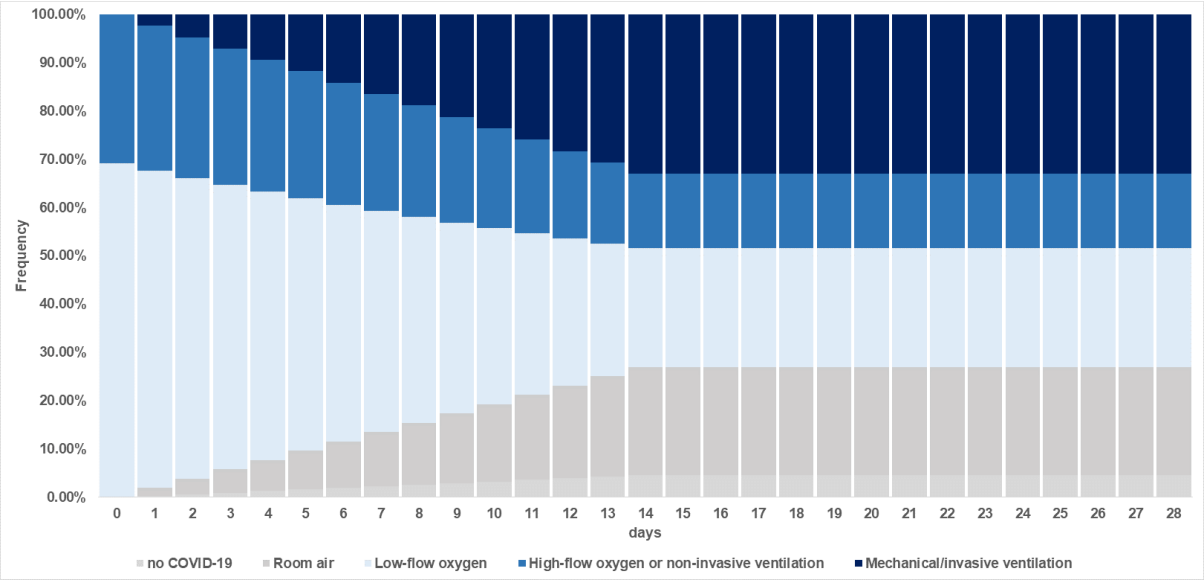
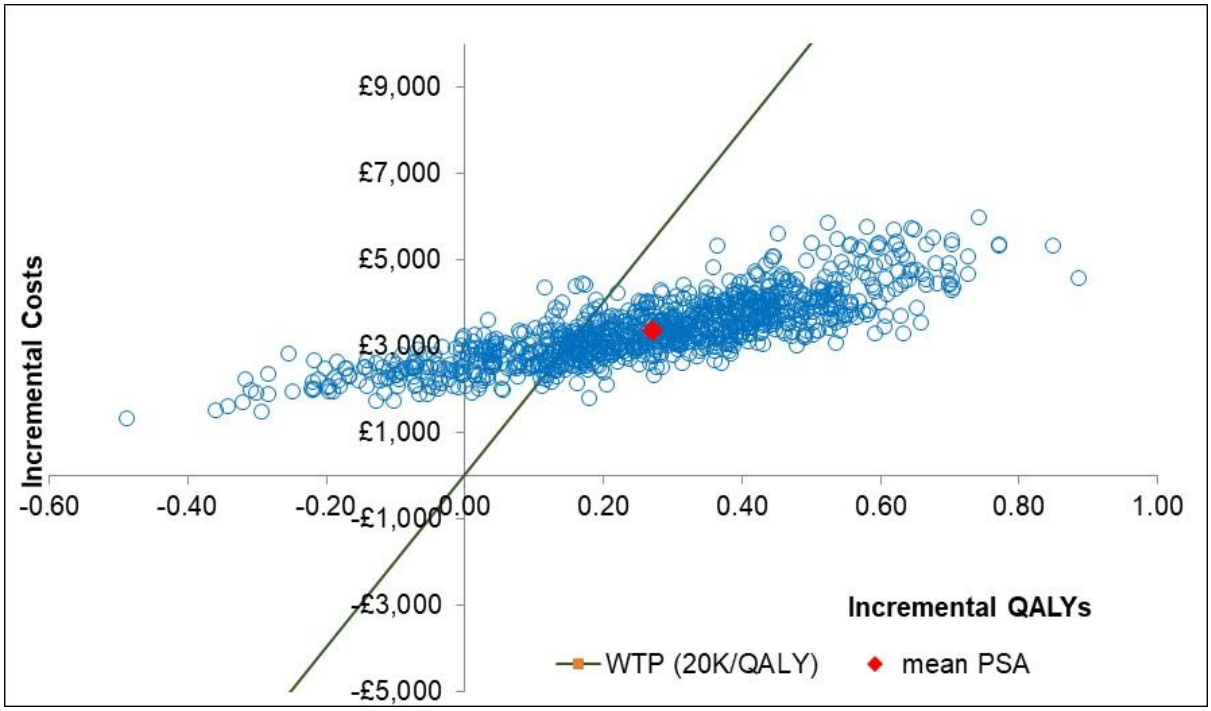
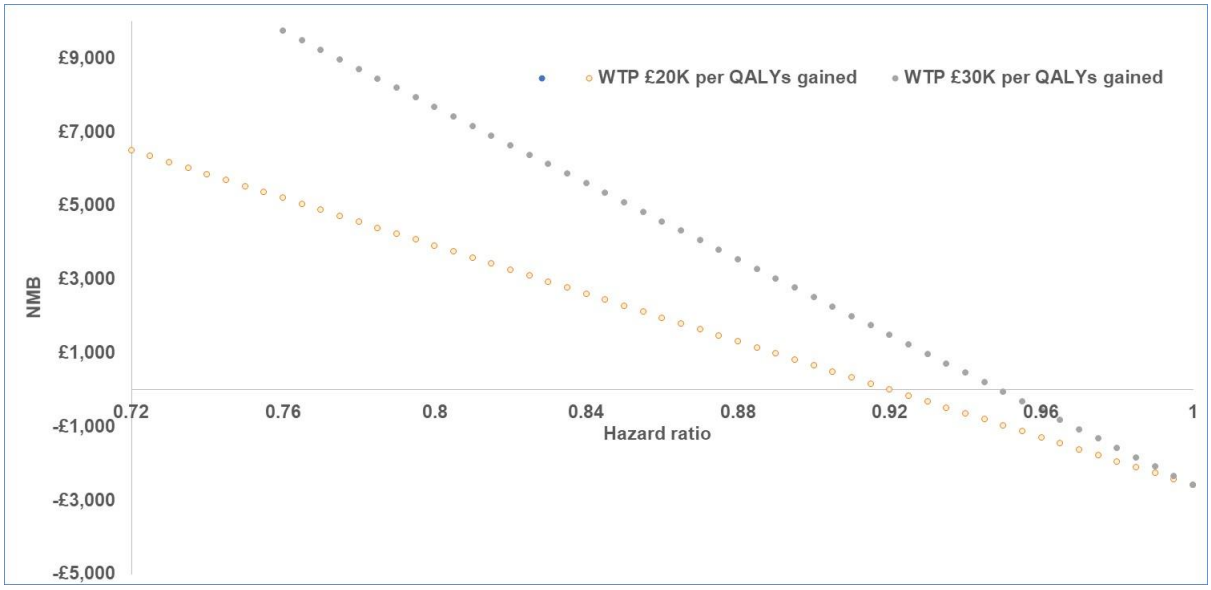


Figure 3: Probabilistic sensitivity analysis cost-effectiveness plane



Abbreviations: PSA: probabilistic sensitivity analysis, QALY: quality adjusted life years; WTP: willingness to pay

Figure 4: Threshold analysis for the treatment effect for overall survival – net monetary benefit at a WTP threshold of £20,000 and £30,000 per QALY gained.



Abbreviations: NMB: net monetary benefit; QALY: quality adjusted life years; WTP: willingness to pay

Table 1: Model input parameters

Parameter	Expected value	Range for sensitivity analysis		Measure of uncertainty	Source
		Lower bound	Upper bound		
Baseline characteristics					
Age	64·5	62·5*	66·5*	Normal (SD: 19·2)	[8]
Gender distribution (female %)	40·1%	40%*	55%*	Beta	[8]
Treatment effect					
HR OS	0·85	0·66	1·09	Lognormal (95% CI)	[6]
HR time to discharge	HR1 (day 0-4): 0·56; HR2 (day 5-9): 1·00; HR3 (day 10-14): 1·07; HR4 (day 15-19): 1·35; HR5 (day 20+): 1·24			Multivariate normal	[6]
Health related QoL – Utility value					
Invasive ventilation	0			Not varied	Assumed
Health related QoL – applied as decrement					
Increased comorbidities at entry	-0·116	0*	0·15*	normal[a]	Derived from[34]
Discharged (first 52 weeks)	-0·097	0·077**	0·116**	normal[a]	[9]
hospitalised, not on oxygen	-0·36	0·288**	0·432**	normal[a]	[25]
hospitalised, on LFO, or HFO or NIV	-0·58	0·464**	0·696**	Normal (95% CI)	[24]
Costs					
RDV – price per vial	£340			Not varied	[20]
SoC – cost per day	£0·53			Not varied	[21]
Hospitalisation cost per day					
hospitalised, not on oxygen and no ongoing care due to COVID	£337	£270**	£405**	Gamma[a]	[19]
hospitalised, not on oxygen and require care due to COVID	£347	£278**	£416**	Gamma[a]	[19]
hospitalised, on LFO	£616	£493**	£739**	Gamma[a]	[19]
hospitalised on HFO or NIV	£933	£747**	£1,120**	Gamma[a]	[19]
hospitalised, on invasive ventilation	£1,518	£1,215**	£1,822**	Gamma[a]	[19]
Medium – long term after discharge					
Elevated risk of death	7·7	7·2	8·3	Lognormal (95% CI)	[8]
MOD QALY loss	-0·023	-0·011***	-0·069***	Beta[a]	Supp Table1
MOD cost	£1,362	£681***	£4,085***	Gamma[a]	Supp Table1
Monitoring one off cost	£364·6	182·3***	1,093·8***	Gamma[a]	Assumed[26, 27]

* Range assumed; ** range assumed to be +/ 20%; *** range assumed to be halved or tripled
[a] SE assumed to be 10%
Abbreviations: CI: confidence interval; HFO = high flow oxygen; HR = hazard ratio; LFO = low flow oxygen; MOD: multi-organ disfunction; NIV = non-invasive ventilation; OS: overall survival; QALY: quality adjusted life years; RDV: remdesivir; SD: standard deviation; SE: standard error; SoC: standard of care

Table 2: Model base-case and secondary scenario results

	Base-case: RDV reduces death								Secondary scenario: RDV does not reduces death*						
	Total costs (£)	**Total LYG (und)**	**Total QALYs**	**Incr. costs (£)**	**Incr. LYG (und)**	**Incr. QALYs**	**ICER (£/QALY)**		**Total costs (£)**	**Total LYG (und)**	**Total QALYs**	**Incr. costs (£)**	**Incr. LYG (und)**	**Incr. QALYs**	**ICER (£/QALY)**
	Deterministic								**Deterministic**						
SoC	£9,386	14·34	6·35	-	-	-	-		£10,311	14·34	6·35	-	-	-	-
RDV	£12,718	14·97	6·63	£3,332	0·64	0·28	£11,881		£11,970	14·34	6·35	£1,659	-	0·00	>£1M
	Probabilistic								**Probabilistic**						
SoC	£9,393	14·34	6·35	-	-	-	-		£10,316	14·33	6·35	-	-	-	-
RDV	£12,758	14·95	6·62	£3,365	0·62	0·27	£12,400		£11,982	14·33	6·35	£1,666	-	0·00002	>£1M
Probability CE 20K per QALY gained							74%								0%

Abbreviations: CE: cost-effective; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; und: undiscounted; QALY: quality adjusted life years; RDV: remdesivir; SoC: Standard of care; >£1M; over £1 million

* In this scenario, RDV the treatment effect for the probability of ventilation in patients initiated on SoC (compared with RDV) is assumed to be same as RDV