THE LANCET
Respiratory Medicine

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Fisher BA, Veenith T, Slade D, et al. Namilumab or infliximab compared with standard of care in hospitalised patients with COVID-19 (CATALYST): a randomised, multicentre, multi-arm, multistage, open-label, adaptive, phase 2, proof-of-concept trial. *Lancet Respir Med* 2021; published online Dec 16. https://doi.org/10.1016/S2213-2600(21)00460-4.

Supplementary Appendix

Namilumab or infliximab compared to standard of care in hospitalised patients with COVID-19 (CATALYST): a phase 2 randomised adaptive trial

Benjamin A. Fisher[1.2.3]*, Tonny Veenith[4,5]*, Daniel Slade[3]*, Charlotte Gaskell[3], Matthew Rowland[6], Tony Whitehouse[4,5], James Scriven[7,8], Dhruv Parekh[4,5,9] Madhu S. Balasubramaniam[10], Graham Cooke[11], Nick Morley[12], Zoe Gabriel[13], Matthew P. Wise[14], Joanna Porter[15], Helen McShane[16], Ling-Pei Ho[17,18], Philip N. Newsome[2,19], Anna Rowe[2.3], Rowena Sharpe[3], David R. Thickett[5,9], Julian Bion[4,5], Simon Gates[3], Duncan Richards[20] and Pamela Kearns[2,3] on behalf of CATALYST investigators

* These authors have made an equal contribution.

Corresponding authors contact details:

Dr Benjamin A. Fisher, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK. Email: b.fisher@bham.ac.uk

Prof. Tonny Veenith, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK. Email: t.v.veenith@bham.ac.uk

1. Rheumatology Research Group, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, UK

2. National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.

3. Cancer Research UK Clinical Trials Unit, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK

4. Department of Critical Care Medicine, University Hospitals Birmingham NHS Trust, United Kingdom

5. Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, UK

6. Kadoorie Centre for Critical Care Research, Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

7. Department of Infectious Diseases, University Hospitals Birmingham NHS Trust, UK

8. Institute of Microbiology and Infection, University of Birmingham, UK.

9. Department of Respiratory Medicine, University Hospitals Birmingham NHS Trust, UK

10. Department of Critical Care Medicine, Royal Bolton Hospital, Bolton, UK

11. Department of Infectious Disease, Imperial College London, London, UK

12. Department of Haematology, Royal Hallamshire Hospital, Sheffield, UK

13. Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

14. Department of Critical Care Medicine, University Hospital of Wales, Cardiff, UK

15. Department of Respiratory Medicine, University College Hospital, London, UK

16. The Jenner Institute, University of Oxford, Oxford, UK

17. MRC Human Immunology Unit, Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, UK

18. Oxford Interstitial Lung Disease Service, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

19. Centre for Liver Research, Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK

20. Oxford Clinical Trials Research Unit, Botnar Research Centre, University of Oxford, Oxford, UK

The CATALYST investigators include the following:

Prof. Tonny Veenith (Chief Investigator, University Hospitals Birmingham), Dr Benjamin A. Fisher (Deputy Chief Investigator, University of Birmingham), Daniel Slade (Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham), Charlotte Gaskell (CRCTU, University of Birmingham), Dr Francis Mussai (University of Birmingham), Prof Gary Middleton (University of Birmingham), Dr Dhruv Parekh (University of Birmingham), Dr Anna Rowe (CRCTU, University of Birmingham), Prof. Duncan Richards (University of Oxford), Dr Mathew Rowland (University of Oxford), Prof. Julian Bion (University of Birmingham), Prof. Simon Gates (Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham), Prof. Pam Kearns (CRCTU, University of Birmingham), Dr Rowena Sharpe (CRCTU, University of Birmingham), Dr Sarah Bowden (CRCTU, University of Birmingham), Prof. David Thickett (University Hospitals Birmingham), Dr Mansoor Bangash (University Hospitals Birmingham), Prof. Fang Gao-Smith (University Hospitals Birmingham), Dr Jaimin Patel (University Hospitals Birmingham), Prof. Elizabeth Sapey (University Hospitals Birmingham), Dr Mark Thomas (University of Birmingham), Prof. Mark Coles (University of Oxford), Prof. Peter Watkinson (University of Oxford), Prof. Naj Rahman (University of Oxford), Prof. Ling-Pei Ho, (University of Oxford), Prof. Brian Angus (University of Oxford), Dr Alexander J. Mentzer (University of Oxford), Dr Alex Novak (University of Oxford), Prof. Marc Feldmann (University of Oxford) Alex Richter (University of Birmingham), Sian Faustini (University of Birmingham).

CRCTU staff: Camilla Bathurst, Joseph van de Wiel, Susie Mee, Karen James, Bushra Rahman, Karen Turner.

Data Monitoring Committee

Member	DMC Role	Contact Information
Professor Adam Hill	Chair	University of Edinburgh
Professor Christina Yap	Independent Statistician	The Institute of Cancer Reserarch, London
Professor Anthony Gordon		Imperial College London

Trial Steering Committee

Member	TSC Role	Contact Information
Professor Michael Matthay	Chair	University of California San Francisco
Professor Danny McAuley	Deputy Chair	Queen's University Belfast
Mr Andrew Hall	Independent Statistician	University of Leeds
Professor Paul Dark		Manchester University
Professor Sir Andrew McMichael		University of Oxford

Scientific Advisory Board

Member		Contact Information
Professor Philip Newsome	Chair	University of Birmingham
Professor Pamela Kearns		University of Birmingham
Professor Tonny Veenith		University of Birmingham
Dr Benjamin Fisher		University of Birmingham

Dr Rowena Sharpe		University of Birmingham
Professor Julian Bion		University of Birmingham
Professor Bryan Williams		University College London
Professor Duncan Richards		University of Oxford
Professor Graham Cooke		Imperial College London
Professor Helen McShane		University of Oxford
Professor Ling-Pei Ho		University of Oxford
Dr Rebecca Turner		University College London
Professor Simon Gates		University of Birmingham
Professor Vincenzo Libri		University College London

Supplementary Text Methods

Participant Eligibility

Exclusion criteria included planned palliative care, pregnancy or breastfeeding, women of childbearing potential and non-vasectomised men who were unwilling to use effective contraception for the duration of the trial and throughout the drug-defined post-trial period, known HIV or chronic hepatitis B or C infection, concurrent immunosuppression with biological agents, a history of haematopoietic stem cell or solid organ transplant, known hypersensitivity to drug products or excipients, tuberculosis or other severe infections such as (non-SARS-CoV-2) sepsis, abscesses, and opportunistic infections requiring treatment, moderate or severe heart failure (NYHA class III/IV), or any other indication or medical history, that in the opinion of the patient's local investigator, made the patient unsuitable for trial participation. Co-enrolment into other interventional trials was not permitted with the exception of the RECOVERY-Respiratory Support trial comparing continuous positive airway pressure or high flow nasal oxygen to standard care, as this met current UK guidance on mechanistic independence in co-enrolment.[19]

Additional detail on randomisation

The in-house system for randomisation was managed by the programming team at the CRCTU. Site research staff would enter data via eCRFs. The system was designed with the capability of turning off arms or allowing for the addition of new arms given the platform nature of the trial. Programming were to be informed of any modifications to be made following the outcome of interim analyses and implemented them accordingly.

Data Handling

The data was stored securely within a relational database with the raw datasets only accessible by the trials team. Data was entered onto the system at sites through the use of eCRFs. The full details remain in the protocol.

Recommendations

CRP data was considered by the data monitoring committee (DMC) in the context of the emerging safety data to make a recommendation as outlined below:

a) If there is strong evidence of an additional anti-inflammatory effect (CRP) and a satisfactory safety profile consider progression to clinical endpoint evaluation whether in this trial or in another one;
b) If there is no evidence of additional biological effect or an unfavourable safety signal, then terminate arm and do not proceed.

Simulations to Inform Sample Size

The simulations and tables below demonstrate the operating characteristics of a trial design with the chosen decision criteria, based on a simpler analysis of the area under the curve for sequential CRP data, with effect sizes informed from a dataset from 1026 hospitalised COVID-19 patients at Queen Elizabeth Hospital, Birmingham. In our simulations, we compared a traditional fixed trial design recruiting 120 patients with candidate adaptive designs. We present basic operating characteristics for the fixed design (Table 6A) and the chosen adaptive design (Table 6B). We studied six scenarios of treatment effect, and estimated, through simulation, the probability of a trial stopping early for "success" or "futility," and ultimately concluding success. Simulations were performed in Fixed and Adaptive Clinical Trial Simulator (FACTS) software using default non-informative priors.

Table A. Operating characteristics for a fixed trial design of 120 patients.

Scenario	Probability stopping early for success	Probability stopping early for futility	Overall probability of success	Mean number of patients
Null	0	0	0.101	120
A	0	0	0.537	120
B	0	0	0.926	120
C	0	0	0.997	120
D	0	0	0.008	120
E	0	0	0	120

Scenarios A, B, and C are beneficial effects of the intervention with (true) treatment effects of 0.25, 0.5 and 0.75 standard deviations, "null" is zero treatment effect and D and E are harmful effects of 0.25 and 0.5 standard deviations. "success" and "futility" are defined as above.

Table B. Operating characteristics for an adaptive design with interim analyses at 40 and 80 patients.

Scenario	Probability stopping early for success	Probability stopping early for futility	Overall probability of success	Mean number of patients
Null	0.148	0.624	0.176	66
A	0.455	0.281	0.559	70
B	0.798	0.089	0.890	59
C	0.965	0.012	0.985	48
D	0.03	0.901	0.031	52
E	0.003	0.986	0.003	43

The adaptive design achieves similar probabilities of success in scenarios where the treatment effect is truly beneficial (A, B and C), and increases the probability of success only slightly if the intervention is harmful (D and E). There is some increase in the probability of success if the treatment effect is zero (Type I error) but this is offset by the very substantial reductions in the numbers of patients needed in all scenarios. Moreover, Type I error is not a serious problem as all interventions would be evaluated further in phase III trials.

Additional information on interim analyses

The interim analyses for the DMC were conducted by the trial statisticians. Only the statisticians and the DMC members, who were independent from the operation of the trial, had access to the results in confidence

Supplementary Text Results

Fitted Model – Namilumab

$$Log(CRP) = 3.41 + a - 0.24 * Time + b + 0.01 * Time^2 - 0.22 * CareStatus + 0.02 * Age + 0.20 * Trt - 0.46 * CareStatus * Trt - 0.09 * Time * Trt + \varepsilon$$

Where

$$a \sim N(0, 0.73^2), b \sim N(0, 0.21^2), \varepsilon \sim N(0, 0.58^2)$$

CareStatus = 1 if on the ward and 0 for ICU, Trt = 1 if receiving Namilumab or 0 if usual care alone

Fitted Model – Infliximab

$$Log(CRP) = 3.70 + a - 0.34 * Time + b + 0.02 * Time^2 - 0.45 * CareStatus + 0.01 * Age - 0.43 * Trt + 0.06 * CareStatus * Trt + 0.06 * Time * Trt + \varepsilon$$

Where

$$a \sim N(0, 0.79^2), b \sim N(0, 0.18^2), \varepsilon \sim N(0, 0.65^2)$$

CareStatus = 1 if on the ward and 0 for ICU, Trt = 1 if receiving Infliximab or 0 if usual care alone

Supplementary Table 1. Summary of protocol changes

Amendment number	Date of approval	Protocol version number	Type of amendment	Summary of amendment
1	**REC:** 14-May-20	n/a	Substantial Amendment	Addition of Oxford and UCL as sites
2	**MHRA:** 29-May-20 **HRA:** 01-Jun-20	3.0	Substantial Amendment	Addition of two new IMPs: Namilumab and Infliximab. Update SOE, amendments to inclusion/ exclusion criteria. Specifically: New exclusion criteria relating to the addition of the new drugs: 1) Known hypersensitivity to drug products or excipients 2) Patients with tuberculosis or other severe infections such as (non-COVID-19) sepsis, abscesses, and opportunistic infections requiring treatment 3) Patients with moderate or severe heart failure (NYHA class III/IV)
3	**REC:** 10-Jun-20	n/a	Substantial Amendment	Addition of new sites
4	**MHRA:** 08-Jun-20	n/a	Substantial Amendment	IMPD update
5	**MHRA:** 12-Jun-20 **REC:** 12-Jun-20	4.0	Substantial Amendment	Amendment to inclusion criteria. Specifically: Inclusion criterion 1 changed to: 'Hospitalised adult (≥16 yrs) patients with a clinical picture strongly suggestive of SARS-CoV-2 pneumonia (confirmed by chest X-ray or CT scan, with or without a positive reverse transcription polymerase chain reaction [RT-PCR] assay)' in order to: • Allow CT imaging as evidence for COVID-19 pneumonia • Allow recruitment of patients with strong clinical suspicion for COVID-19 pneumonia but with negative PCR assay Non-substantial amendments to Sample Collection Sub-study text.
6	**MHRA:** 19-Jun-20 **REC:** 20-Jun-20	5.0	Substantial Amendment	Amendment to exclusion criteria. Specifically: 'Concurrent immunosuppression with biological agents or prednisone dose > 20mg' Was changed to 'Concurrent immunosuppression with biological agents' in order to allow patients to be recruited on dexamethasone, following the RECOVERY data
7	**MHRA:** 12-Oct-20 **REC:** 12-Oct-20	6.0	Substantial Amendment	Change of Primary and Secondary Outcomes Specifically: Primary outcome changed to CRP (previously a secondary outcome) from the oxygen saturation to fractional inspired oxygen concentration (SpO2/FiO2) ratio, which now becomes a secondary outcome Hospital free days added as a secondary outcome Overall survival listed as a safety measure (previously death included under hospital survival status as a clinical outcome) Applicable changes to Inclusion/ Exclusion Criteria Specifically: Inclusion criteria changed from 'Oxygen saturation (SaO2) of ≤94% while breathing ambient air or a ratio of the partial pressure of Oxygen (PaO2) to the fraction of inspired oxygen (FiO2) (PaO2:FiO2) ≤ 300 mg Hg (≤40kPa'), to 'CRP ≥40' The following exclusion criteria that relate to the unopened Myelotarg arm were removed from general exclusion and made arm specific: • Known veno-occlusive disease • Neutrophil count < 2 x 109/l or White Blood Cell Count < 4.0 x 109/l The following exclusion criteria was removed as it was felt to be unnecessarily hindering recruitment: • Chronic Obstructive Pulmonary Disease (known FEV1 < 50% predicted or ambulatory or long term oxygen therapy

				Inclusion of Abbreviations list and eCRF table Update to Statistical Analysis section • Justification for CRP, operating characteristics and decision rules

Supplementary Table 2 World Health Organisation Clinical Progression Scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised; mild disease	Hospitalised; no oxygen therapy	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised; severe disease	Hospitalised; oxygen by NIV or high flow	6
	Intubated and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) **or** vasopressors	8
	Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) **and** vasopressors, dialysis or ECMO	9
Death	Dead	10

Adapted from WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020;20:e192-e197.

Footnotes for use in CATALYST

1. If pO_2 not available then use the SpO_2/FiO_2 ratio instead

2. For pO_2 measurements in kPa, use an online calculator e.g. https://www.msdmanuals.com/en-gb/medical-calculators/PaO_2_FiO_2Ratio.htm to calculate a pO_2/FiO_2 ratio equivalent to that obtained with pO_2 measured in mmHg, or else consider an equivalent ratio to 200, when dividing pO_2 in kPa by FiO_2, is 26.7, and an equivalent to 150 is 20.

3. If medically fit for discharge, record status as for ambulatory patient

4. Asymptomatic implies a return to baseline symptomatic state, i.e. no fever, and no cough, shortness of breath, confusion, myalgia, diarrhoea, fatigue, or weakness above what the participant would have experienced on a daily basis before their COVID-19 episode

5. Symptomatic but independent, implies that the participant has some of the additional symptoms as above, but needs no additional help with activities of daily living above what they required prior to their COVID-19 episode.

6. Symptomatic but needs assistance, implies that in addition to having symptoms as above, they require help with activities of daily living i.e. bathing/showering, personal hygiene and combing of hair, dressing, toileting, mobility/transferring and self-feeding, above what they required on a daily basis prior to their COVID-19 episode.

7. Score 0 (uninfected: no viral RNA detected) is not being assessed as part of CATALYST.

Supplementary Table 3. Point estimates and associated 95% credible intervals for mean posterior predictive expected ln(CRP) values on days 1, 7 and 14 for ward and ICU patients allocated to usual care alone or namilumab plus usual care and for the differences between these groups (Δ). Conditional effects data derived from Bayesian multi-level regression.

Care Status	Day	Usual Care (Control)	Usual Care + Namilumab	Δ
Intensive Care Unit	1	4.39 (4.02, 4.77)	4.59 (4.25, 4.93)	0.2 (-0.3, 0.7)
Intensive Care Unit	7	3.26 (2.75, 3.73)	2.91 (2.44, 3.37)	-0.35 (-1.02, 0.35)
Intensive Care Unit	14	2.74 (1.82, 3.62)	1.74 (0.82, 2.65)	-1.00 (-2.26, 0.26)
On Ward	1	4.17 (3.86, 4.48)	3.91 (3.62, 4.21)	-0.26 (-0.67, 0.17)
On Ward	7	3.04 (2.60, 3.49)	2.23 (1.77, 2.68)	-0.81 (-1.45, -0.18)
On Ward	14	2.53 (1.64, 3.41)	1.06 (0.13, 1.97)	-1.96 (-4.92, 0.79)

Supplementary Table 4. Point estimates and associated 95% credible intervals for mean posterior predictive expected ln(CRP) values on days 1, 7 and 14 for ward and ICU patients allocated to usual care alone or infliximab plus usual care and for the differences between these groups (Δ). Conditional effects data derived from Bayesian multi-level regression.

Care Status	Day	Usual Care (Control)	Usual Care + Infliximab	Δ
Intensive Care Unit	1	4.58 (4.09, 5.09)	4.15 (3.58, 4.72)	-0.43 (-1.19, 0.32)
Intensive Care Unit	7	3.21 (2.62, 3.80)	3.13 (2.44, 3.81)	-0.08 (-0.99, 0.82)
Intensive Care Unit	14	3.33 (2.26, 4.35)	3.66 (2.46, 4.79)	0.32 (-1.19, 1.77)
On Ward	1	4.13 (3.72, 4.54)	3.76 (3.35, 4.16)	-0.37 (-0.94, 0.20)
On Ward	7	2.76 (2.23, 3.30)	2.74 (2.19, 3.27)	-0.02 (-0.79, 0.73)
On Ward	14	2.88 (1.86, 3.89)	3.27 (2.17, 4.29)	0.52 (-2.15, 2.94)

Supplementary table 5. Point estimates of the probability of being at each level of the WHO Clinical progression score on days 1, 14 and 28 for ward and ICU patients allocated to usual care alone or namilumab plus usual care. Conditional effects data derived from Bayesian longitudinal proportional odds ordinal regression.

			WHO score level									
	Care Status	Day	1	2	3	4	5	6	7	8	9	10
Usual Care (Control)	Intensive Care Unit	1	0.00	0.01	0.00	0.01	0.10	0.28	0.23	0.16	0.17	0.04
	Intensive Care Unit	14	0.03	0.13	0.03	0.06	0.22	0.20	0.08	0.05	0.07	0.14
	Intensive Care Unit	28	0.18	0.26	0.03	0.05	0.10	0.09	0.04	0.02	0.03	0.19
	On Ward	1	0.00	0.12	0.04	0.11	0.35	0.27	0.08	0.02	0.01	0.00
	On Ward	14	0.09	0.39	0.05	0.08	0.14	0.08	0.05	0.04	0.04	0.04
	On Ward	28	0.31	0.31	0.02	0.04	0.07	0.04	0.02	0.02	0.03	0.14
Usual Care + Namilumab	Intensive Care Unit	1	0.00	0.01	0.00	0.01	0.10	0.29	0.23	0.16	0.16	0.04
	Intensive Care Unit	14	0.06	0.26	0.04	0.09	0.21	0.12	0.05	0.04	0.07	0.08
	Intensive Care Unit	28	0.34	0.30	0.02	0.03	0.06	0.05	0.02	0.01	0.03	0.13
	On Ward	1	0.00	0.12	0.05	0.12	0.35	0.26	0.07	0.02	0.01	0.00
	On Ward	14	0.18	0.48	0.03	0.05	0.08	0.07	0.04	0.02	0.02	0.03
	On Ward	28	0.54	0.22	0.01	0.02	0.03	0.03	0.03	0.02	0.03	0.07

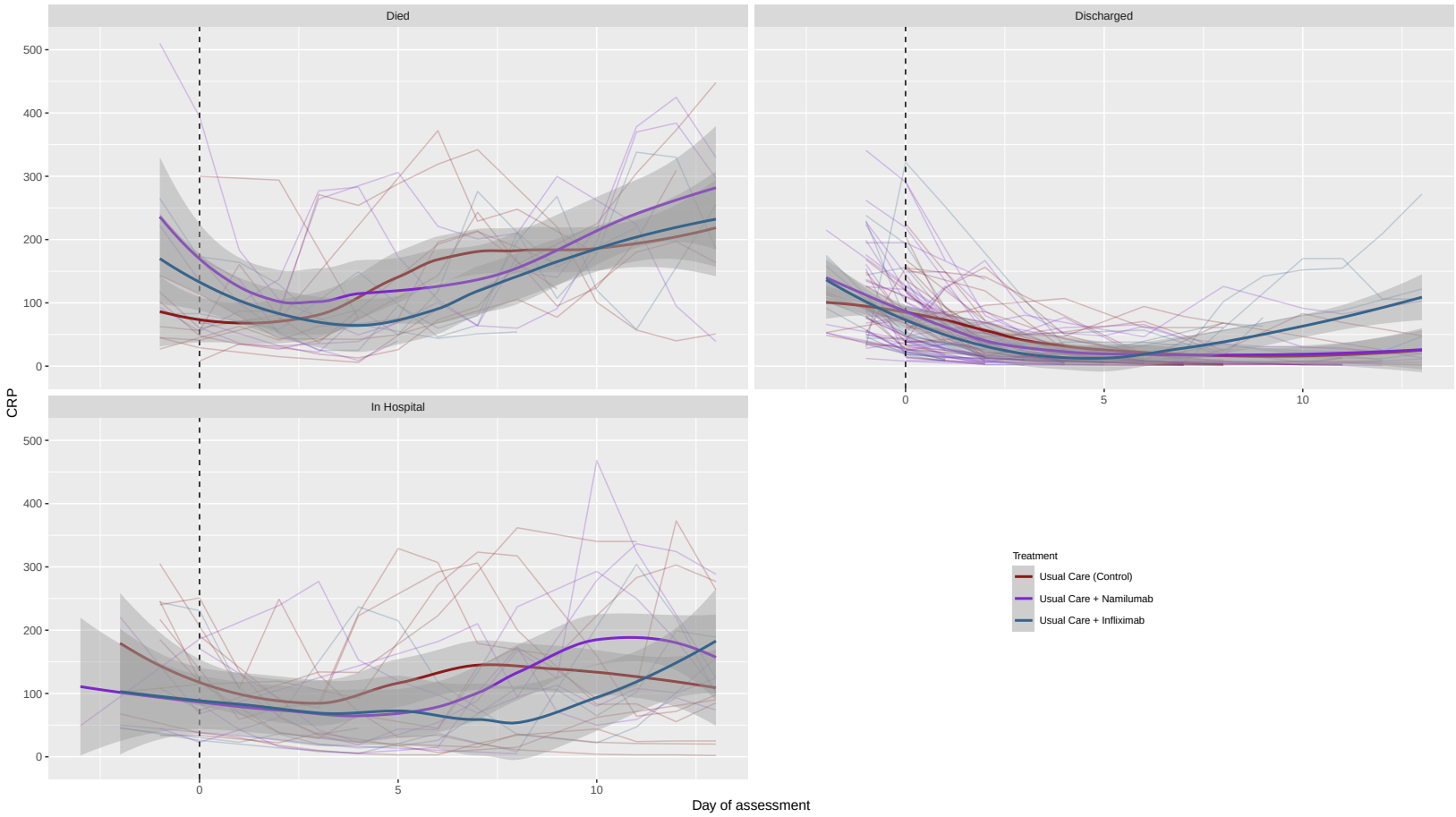
Supplementary table 6. Point estimates of the probability of being at each level of the WHO Clinical progression score on days 1, 14 and 28 for ward and ICU patients allocated to usual care alone or infliximab plus usual care. Conditional effects data derived from Bayesian longitudinal proportional odds ordinal regression.

			WHO score level									
	Care Status	Day	1	2	3	4	5	6	7	8	9	10
Usual Care (Control)	Intensive Care Unit	1	0.00	0.00	0.00	0.01	0.06	0.21	0.26	0.25	0.14	0.07
	Intensive Care Unit	14	0.03	0.15	0.07	0.08	0.18	0.18	0.09	0.05	0.04	0.14
	Intensive Care Unit	28	0.21	0.28	0.06	0.05	0.07	0.08	0.04	0.02	0.01	0.17
	On Ward	1	0.00	0.09	0.09	0.13	0.28	0.27	0.10	0.02	0.00	0.00
	On Ward	14	0.11	0.42	0.09	0.07	0.09	0.05	0.04	0.05	0.04	0.03
	On Ward	28	0.40	0.28	0.04	0.03	0.04	0.02	0.02	0.02	0.01	0.13
Usual Care + Infliximab	Intensive Care Unit	1	0.00	0.00	0.00	0.01	0.08	0.23	0.26	0.24	0.12	0.05
	Intensive Care Unit	14	0.02	0.12	0.05	0.07	0.18	0.19	0.10	0.07	0.04	0.15
	Intensive Care Unit	28	0.16	0.24	0.06	0.06	0.09	0.09	0.05	0.04	0.02	0.19
	On Ward	1	0.00	0.12	0.10	0.14	0.29	0.25	0.08	0.02	0.00	0.00
	On Ward	14	0.09	0.39	0.10	0.08	0.10	0.07	0.05	0.04	0.04	0.05
	On Ward	28	0.31	0.31	0.05	0.04	0.05	0.04	0.02	0.02	0.02	0.14

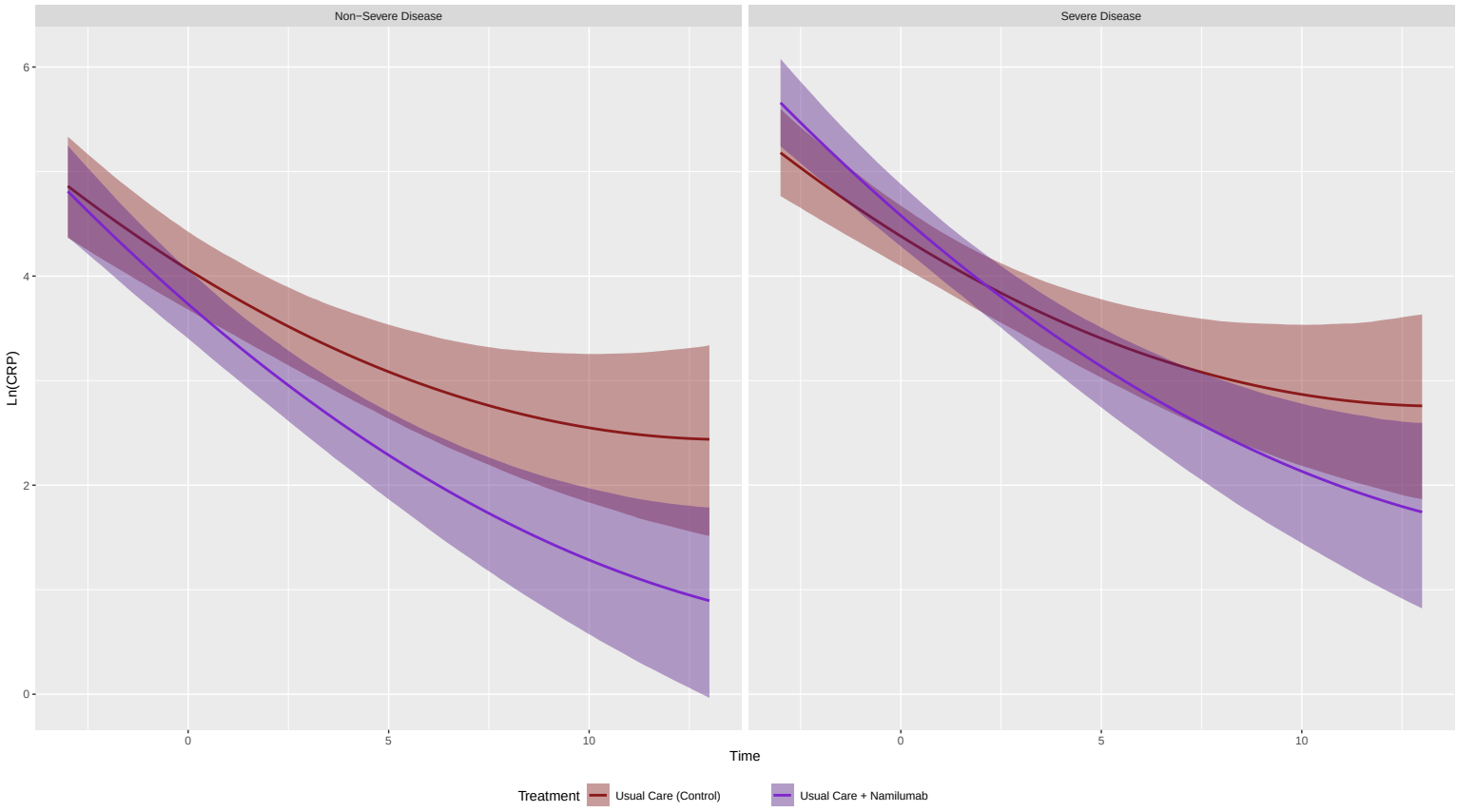
Supplementary Table 7. Total recorded adverse events, SAEs and deaths due to any cause. Specific diagnoses relate to adverse events that are CTCAE grade ≥3, secondary infection or allergic reaction. Only events occurring at least twice within an active drug/usual care comparison are shown. Data shown are number of adverse event occurrences (number of patients affected) in the safety population.

	Namilumab		**Infliximab**	
	Usual care n=54	Active arm n=55	Usual care n=34	Active arm n=29
Total reported adverse events (all grades)	145 (29)	134 (30)	112 (17)	102 (20)
Total adverse events (CTCAE grade ≥3, secondary infection or allergic reaction)	115 (24)	132 (25)	102 (16)	79 (16)
Total infection events	10 (7)	20 (8)	7 (4)	4 (4)
SAEs	10 (10)	10 (10)	5 (5)	6 (6)
Deaths	10 (10)	6 (6)	5 (5)	4 (4)
Anaemia	10 (6)	10(6)	8 (5)	2 (2)
Sinus bradycardia	2 (1)	0 (0)	2 (1)	0 (0)
Multiorgan failure	3 (3)	1 (1)	-	-
Covid pneumonia/pneumonitis	5(5)	4(4)	2 (2)	2 (2)
Lung infection	2(2)	1(1)	-	-
Pleural infection	2(1)	0(0)	2 (1)	0 (0)
Sepsis	1(1)	2(2)	-	-
Raised ALT	3(3)	5(5)	1 (1)	1 (1)
Raised Troponin I	0(0)	2(1)	-	-
Raised Creatinine	2(2)	4(3)	2(2)	2(1)
Raised CRP	5(4)	2(2)	5(4)	0(0)
Raised d-dimers	6(5)	3(3)	5(4)	1(1)
Raised ferritin	7(6)	5(5)	5(4)	11(7)
Low lymphocytes	16(12)	5(3)	11 (8)	4 (2)
Raised monocytes	0(0)	3(2)	-	-
Raised neutrophils	9(5)	5(3)	9 (5)	4 (4)
Raised white cells	9(6)	7(4)	9 (6)	9 (5)
Low platelets	1(1)	1(1)	-	-
Raised urea	9(7)	11(5)	8(6)	8(5)
Raised potassium	6(5)	1(1)	4(3)	2(1)
Raised sodium	1(1)	2(1)	-	-
Raised triglycerides	3(3)	1(1)	2(2)	6(4)
Low albumin	15 (13)	11 (7)	12 (10)	13 (8)
Low sodium	2(2)	1(1)	2(2)	2(2)
ARDS	-	-	1(1)	1(1)
Hypotension	-	-	0(0)	2(2)

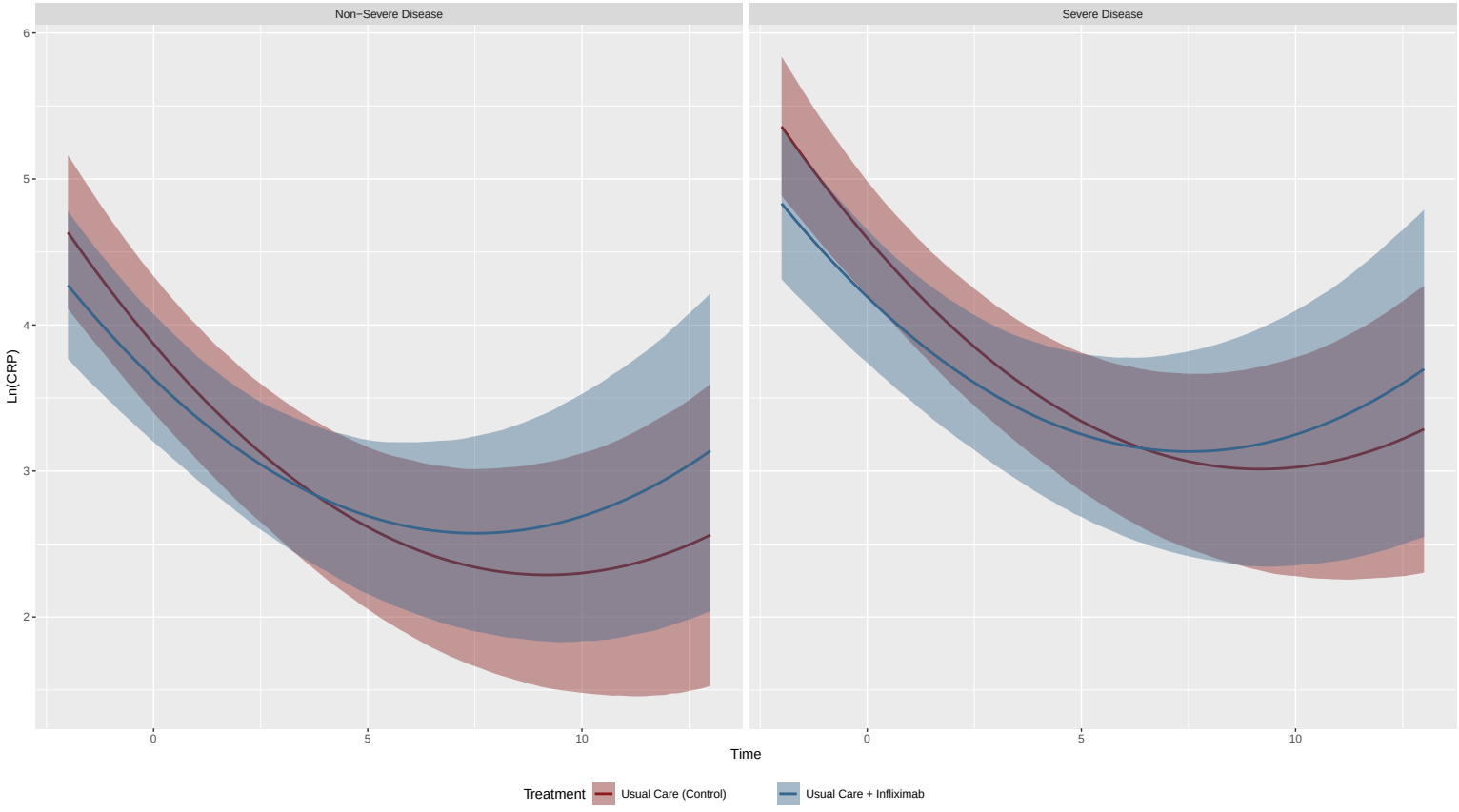
Supplementary Figure 1. CRP over time in relation to day 28 outcomes of death, discharge, and ongoing hospitalisation within the whole CATALYST modified intention to treat population.



Supplementary Figure 2. Conditional effects plots of CRP modelled over time in patients recruited in with non-severe and severe disease at baseline for namilumab (A) and infliximab (B). Severe disease was defined as the use of non-invasive or invasive ventilation or high flow nasal oxygen at baseline. Time 0 is day 1 of assessment.

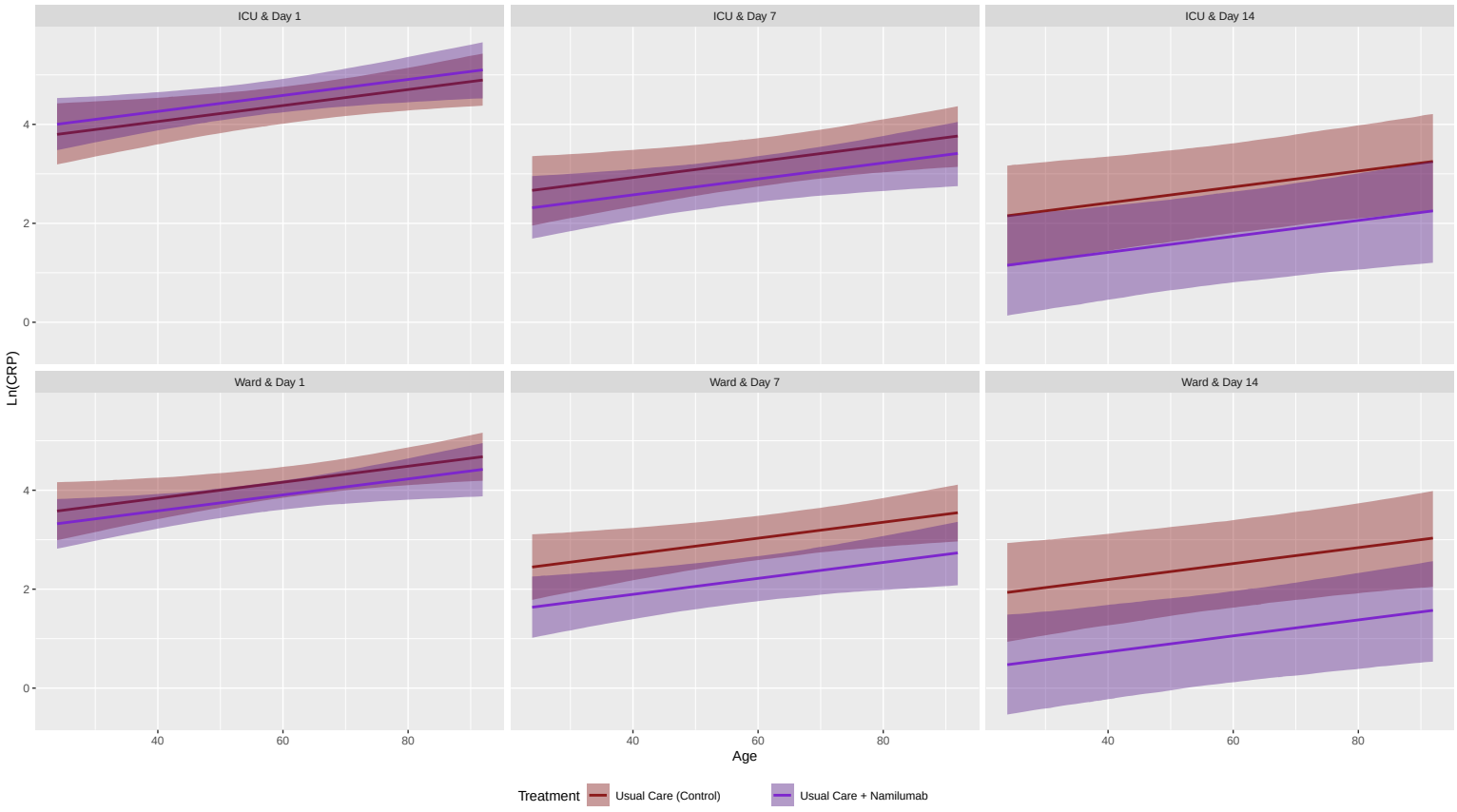


(a)

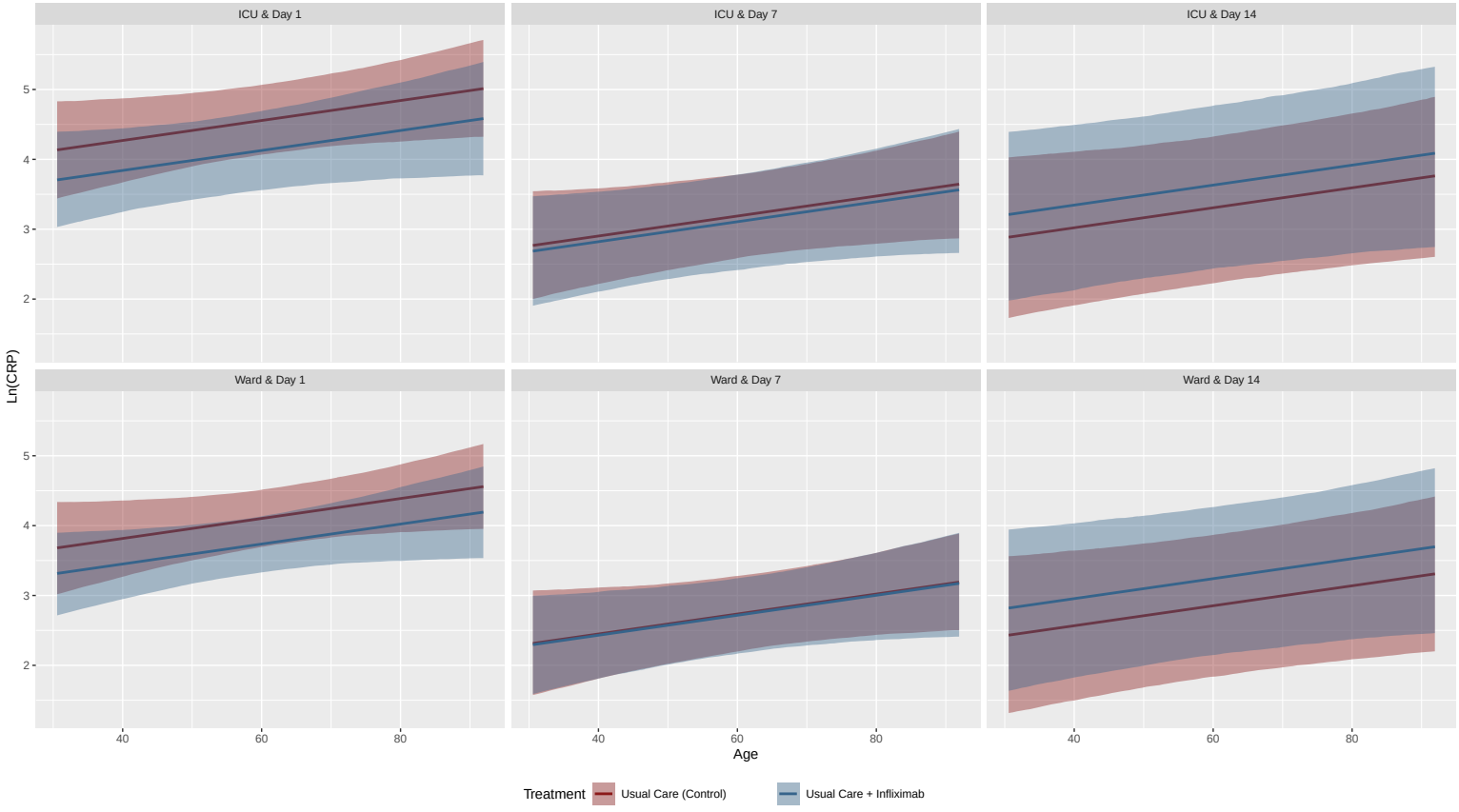


(b)

Supplementary Figure 3. Conditional effects model of CRP in relation to age and treatment at days 0, 7 and 14 in ward and ICU groups. CRP is associated with age but the effect of (A) namilumab and (B) infliximab on CRP is independent of age.

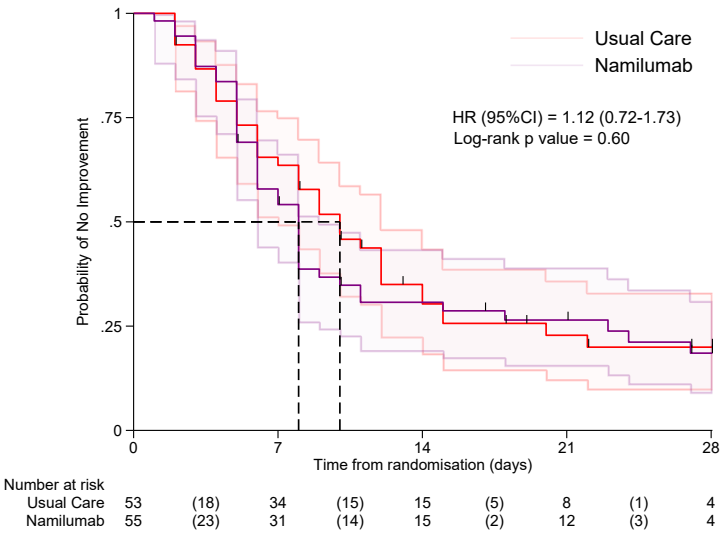


(a)

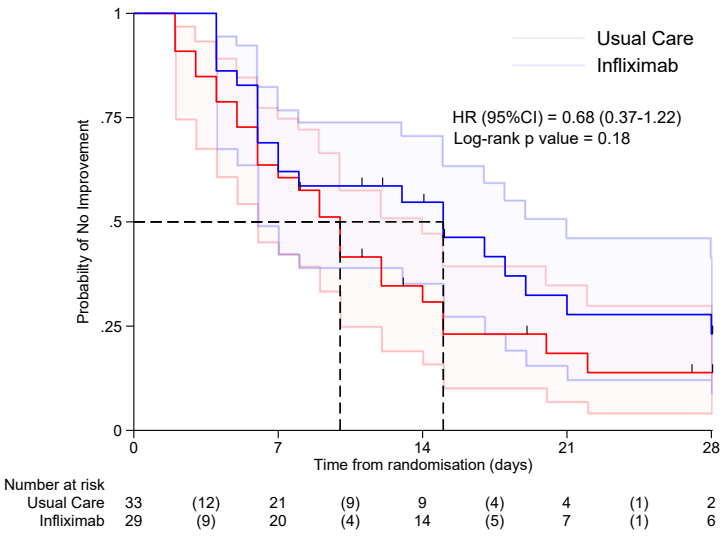


(b)

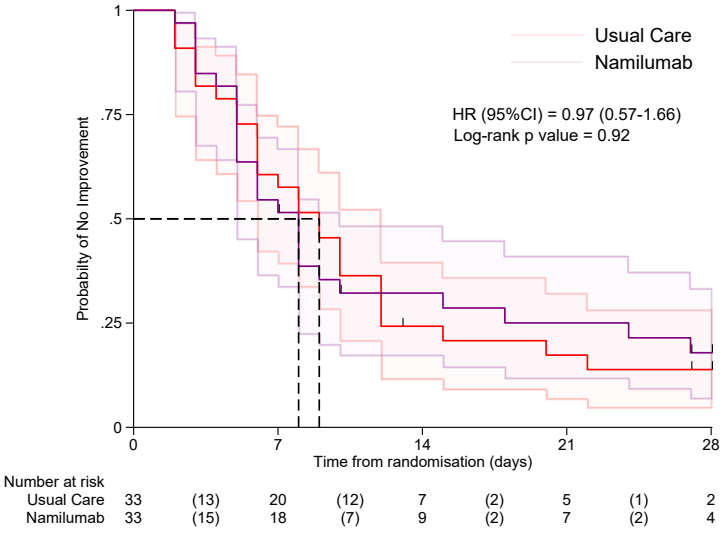
Supplementary Figure 4. Kaplan-Meier plots for time to 2 point improvement for whole population (A, B), ward (C, D) and ICU (E, F) for namilumab (A, C, E) and infliximab (B, D, F).



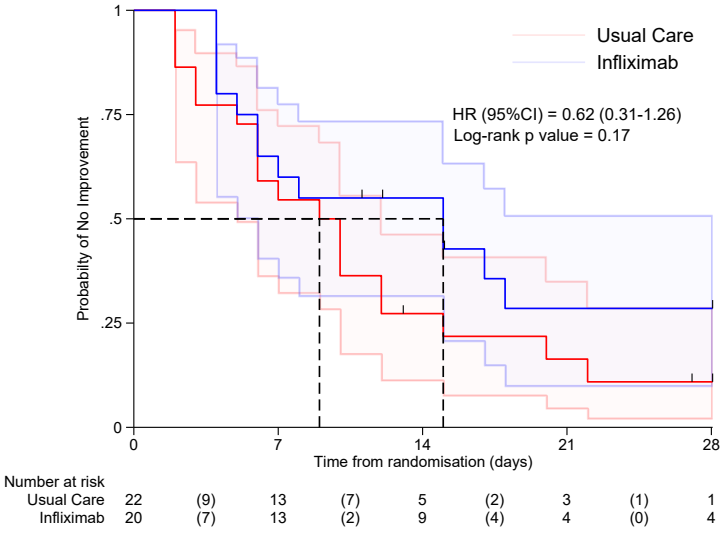
(a)



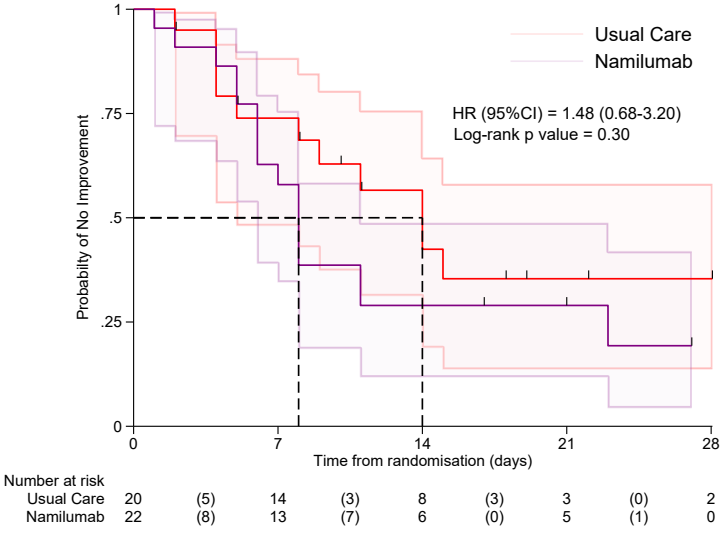
(b)



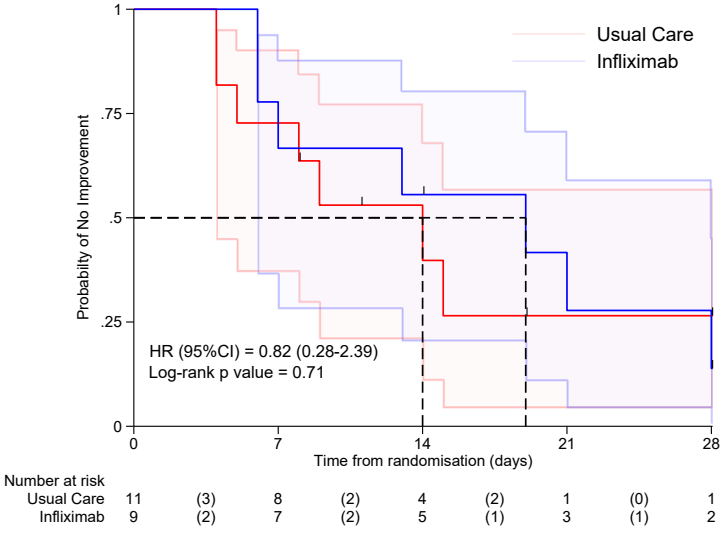
(c)



(d)

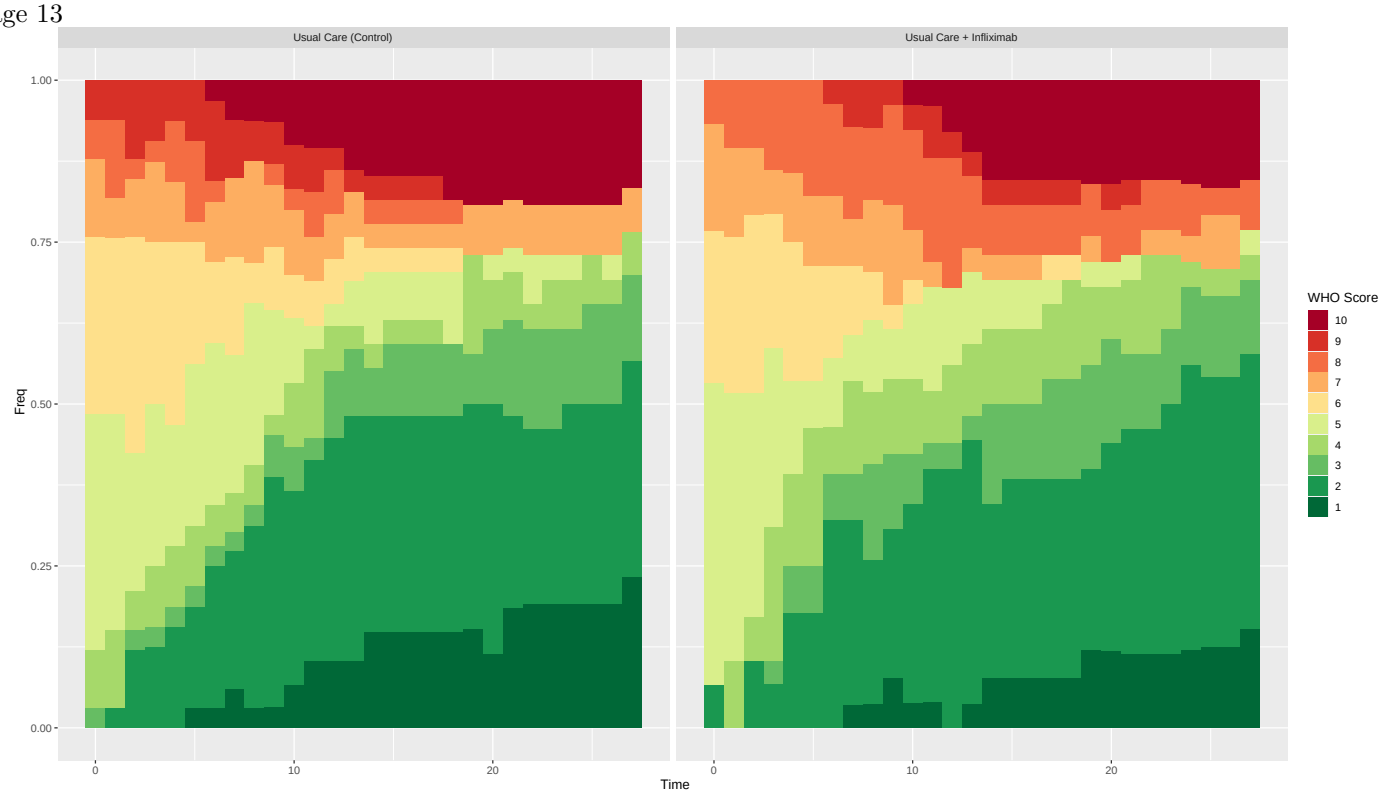


(e)

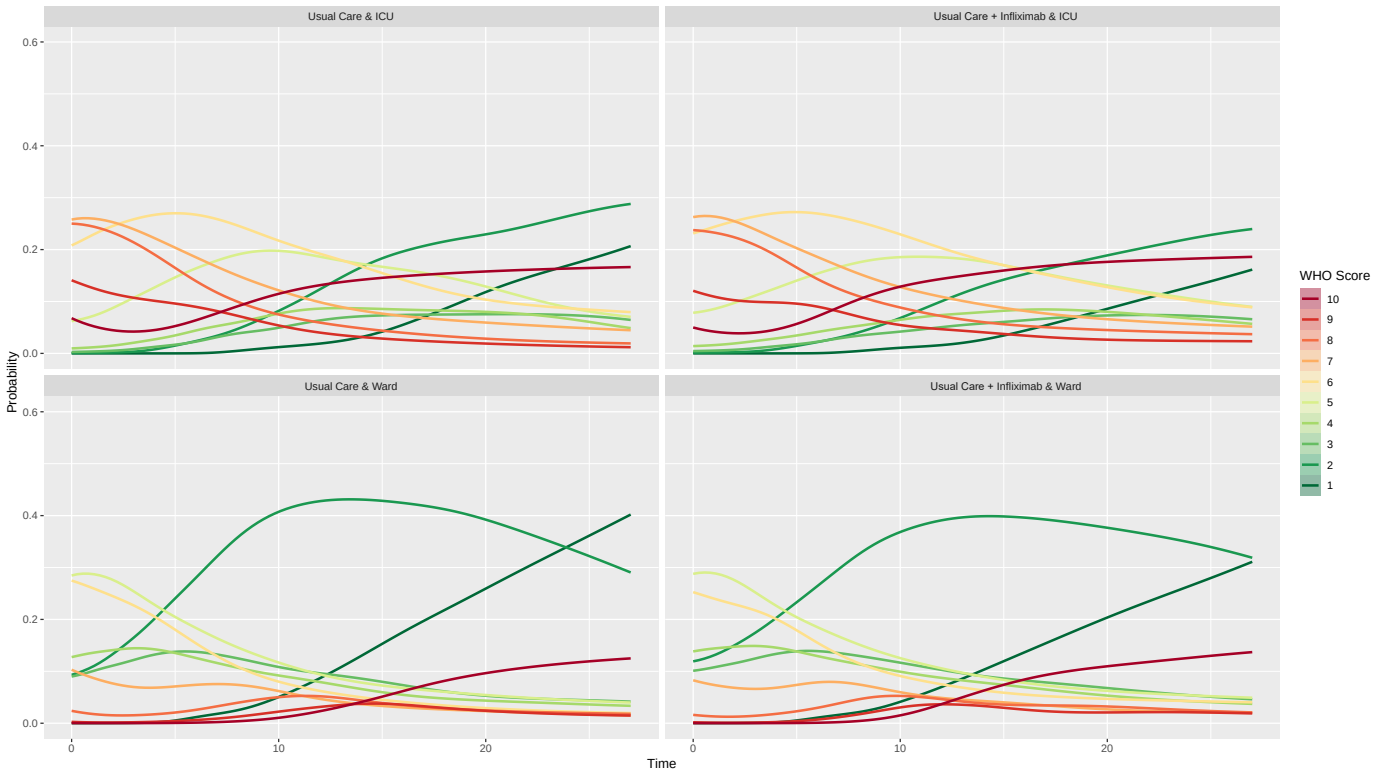


(f)

Supplementary Figure 5. WHO clinical progression score over 28 days for usual care versus infliximab. A, stacked bar chart of raw data for whole population eligible for comparison. B, conditional effects plots of WHO score modelled over time in days showing the probability of being at each level on each day for patients recruited in ICU and ward.

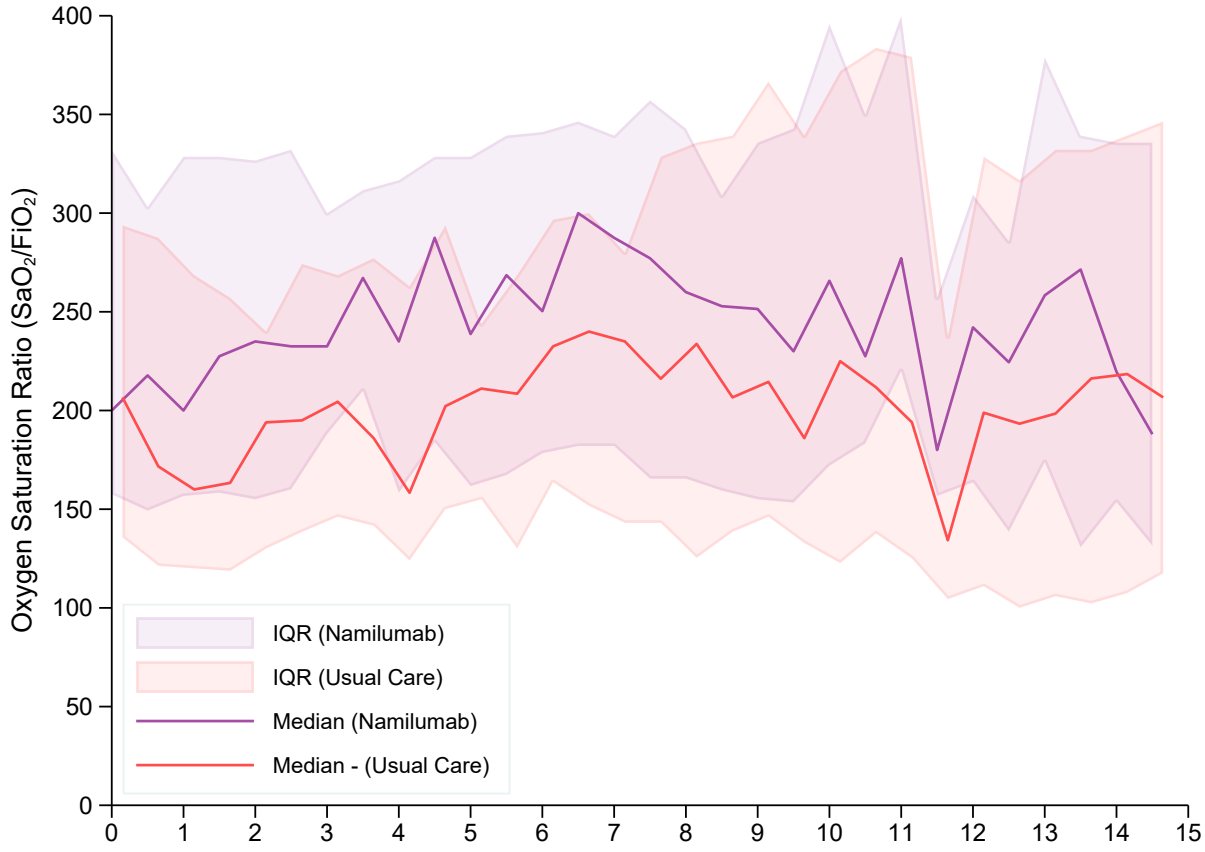


(a)

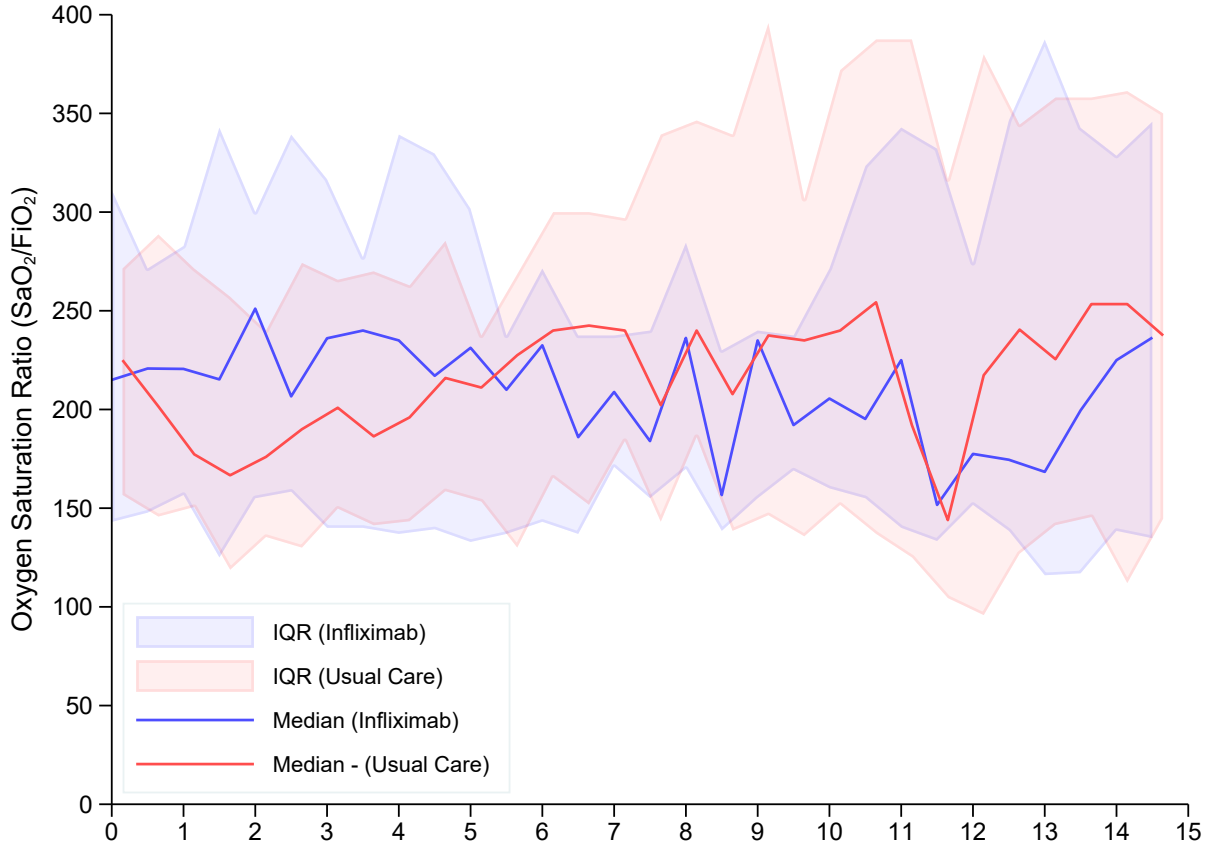


(b)

Supplementary Figure 6. Median oxygen saturation to fraction of inspired oxygen ratio (SF ratio) over time (days) for (A) namilumab (n=55 namilumab and n=54 usual care) and (B) infliximab (n=34 usual care and n=29 infliximab). Higher values indicate better oxygenation status.



(a)



Statistical Analysis Plan

A randomised phase II proof of principle multi-arm multi-stage trial designed to guide the selection of interventions for phase III trials in hospitalised patients with COVID-19 infection.

Version: 2.0
March 17, 2021

Sponsor(s): University of Birmingham
EudraCT Number: 2020-001684-89
Sponsor Reference Number: RG_20-030

Author(s):	
Name:	Mr Daniel Slade
Trial role:	Statistical Lead
Name:	Miss Charlotte Gaskell
Trial role:	Trial Statistician
Name:	Professor Simon Gates
Trial role:	Statistical Lead & Co-Investigator

Reviewed & Approved by:	
Name:	Dr. Benjamin Fisher
Trial role:	Acting Chief Investigator

Key personnel involved in the Statistical Analysis Plan:

Name	Trial role
Mr Daniel Slade	Statistical Lead
Miss Charlotte Gaskell	Trial Statistician
Dr. Tonny Venith	Chief Investigator
Dr. Benjamin Fisher	Deputy Chief Investigator
Professor. Simon Gates	Statistical Lead & Co-Investigator

Document Control Sheet:

Statistical Analysis Plan version:	Reason for update:
v1.0	Initial Version
v2.0	Incorporation of joint-modelling and AUC approach for the primary analysis, complimentary analyses to attempt to take account of censoring. Addition of ITT analysis for secondary endpoints and MITT definition for secondary endpoints. Modification of primary analysis to state inference will be based on only the interaction term of the model. Specification of subgroup analyses based on disease severity, a request of the DMC.

Contents

1 INTRODUCTION **4**
1.1 Purpose of the Statistical Analysis Plan 4
1.2 Summary of the Trial 4

2 TIMING AND REPORTING OF INTERIM AND FINAL ANALYSES **6**

3 RECRUITMENT AND RANDOMISATION **6**
3.1 Recruitment 6
3.2 Randomisation 6
3.3 Ineligible Patients 6

4 DATA QUALITY **6**
4.1 Data Quality: CRFs 6
4.2 Return Rates: CRFs 6

5 TRIAL POPULATION **7**
5.1 Patient Characteristics 7
5.2 Definition of Populations for Analysis 7

6 TREATMENT RECEIVED **7**

7 SAFETY ANALYSIS **7**

8 ANALYSIS **7**
8.1 Analysis of Primary Outcome Measure 8
8.2 Analysis for Secondary Outcome Measures 8
8.3 Subgroup Analysis 9

9 SAMPLE SIZE **9**

10 STATISTICAL SOFTWARE **10**

11 STORAGE AND ARCHIVING **10**

1 INTRODUCTION

1.1 Purpose of the Statistical Analysis Plan

This Statistical Analysis Plan (SAP) provides guidelines for the analysis and presentation of results for the Catalyst trial. This plan, along with all other documents relating to the analysis of this trial, will be stored in the 'Statistical Documentation' section of the Trial Master File. The statistical analysis will be carried out by the trial Statisticians.

1.2 Summary of the Trial

Trial Design
Catalyst is a rapid, open-label, phase II, multi-arm, multi-stage trial permitting an efficient evaluation of the potential efficacy of these targeted drugs which can then be considered for larger-scale testing by one of the current national platform trials.

Objectives
Primary Objectives

- To investigate whether candidate treatments demonstrate evidence of greater attenuation of inflammation as defined by an improvement in C-reactive protein (CRP) concentrations compared with usual care in COVID-19 patients.
- To recommend drugs that should be evaluated further in one of the phase III trials.

Outcome Measures
Primary Outcome Measures

- C-reactive protein measured over time up to day 14 for each patient.

Secondary Outcome Measures

- World Health Organisation (WHO) Clinical Progression improvement Scale (1-10 scale; for the purposes of this trial level 0, no viral RNA detected, will not be assessed)
- The ratio of the oxygen saturation to fractional inspired oxygen concentration (SpO2/FiO2), measured from randomisation to day 14, hospital discharge or death. SpO2 and FiO2 are measured as part of routine clinical care
- Respiratory rate
- Body temperature
- NEWS-2 score
- Length of hospital stay
- Hospital survival status at day 28 / hospital free days
- Proportion of patients discharged at day 28
- Destination of discharge
- Lymphocyte and Neutrophil counts and ratios
- Ferritin, D-Dimer and LDH
- Adverse events (AEs) and Serious Adverse Events (SAEs) as recorded by Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 of grade $\geq$3 with interest in veno-occlusive disease (VOD), secondary infection and allergic reaction
- Overall Survival

Exploratory Outcome Measures

- Blood inflammatory mediators, biomarkers, transciptome and cellular immunology in relation to COVID-19 infection
- Viral load
- Host DNA assessed at baseline to assess for predictors of disease severity and drug response
- blood biomarkers of aveolar epithelial cell damage to include surfactant D and RAGE

Patient Population
This trial seeks to recruit hospitalised patients with COVID-19 who are hypoxic, admitted to either a hospital ward or ICU, and are at risk of deterioration.

Sample Size
A total of up to 60 patients per treatment arm will be recruited.

2 TIMING AND REPORTING OF INTERIM AND FINAL ANALYSES

There two planned interim analyses for the primary endpoint at n=20 and n=40 per arm respectively. Data analyses pertaining to trial conduct, data quality and patient safety will be supplied in confidence to an independent DMC throughout the period the trial is running. The DMC shall review the available data on a proposed 3 monthly basis.

The final analyses for the trial will be conducted once the end of trial has been reached. The final analyses will incorporate the primary, secondary and all exploratory outcomes as detailed in this analysis plan. The end of trial is defined as 6 months after the last data capture.

3 RECRUITMENT AND RANDOMISATION

3.1 Recruitment

At the point of analysis the following data will be reported:

- Date of the database snapshot used for recruitment analysis
- Total number of patients who have been recruited into the trial and randomised to each treatment arm
- Recruitment over time (monthly and cumulative)
- Recruitment by site

3.2 Randomisation

Patients will be randomised 1:1 between Usual Care (Control Arm) and interventional arms using the minimisation procedure described by Pocock and Simon, with a single stratification variable with two levels; Care status: 'On ward' or 'ICU'. Patients will be randomised into either a control group or to receive interventional treatments that are available at their site.

3.3 Ineligible Patients

Ineligible patients are defined as those registered patients who are subsequently found to not meet the eligibility criteria of the trial after being recruited. The proportion of ineligible patients and reasons for their ineligibility will be reported for each treatment arm. In addition the number of patients who were screened in total will be reported along with the number of patients not recruited to the trial and their associated reasons e.g. ineligible.

4 DATA QUALITY

4.1 Data Quality: CRFs

Patient data is collected using case report forms (CRFs) and electronic case report forms (eCRFs). Data collected in this way will be stored on a trial database. The trial database will be checked for missing data and any discrepancies at least annually but prior to any analysis as according to the trial specific data validation plan, which will be developed by both the trial statisticians and the trial coordinator.

4.2 Return Rates: CRFs

The proportion of returned CRFs compared to those that were expected will be reported for each case report form.

5 TRIAL POPULATION

5.1 Patient Characteristics

A summary of patient characteristics will be reported. Descriptive statistics will be provided in the summary including counts and percentages for categorical data items and mean (sd), median and ranges for continuous data items.

5.2 Definition of Populations for Analysis

Safety Population - Safety population will include all patients who receive any trial treatment. For interventional arms this requires the patient to have received some IMP.

MITT Population - The Modified Intention-To-Treat population for the primary analyses will include all patients who receive any trial treatment and who have a baseline CRP measurement and at least one further CRP measurement post baseline. For the secondary endpoints, this includes all patients who receive any trial treatment and have available data for the respective outcome measure.

ITT Population - This includes all randomised patients in their treatment arms, that have available data for the respective outcome measure.

6 TREATMENT RECEIVED

For each treatment arm, the proportion of participants who received treatment as per protocol will be reported. The proportion of participants who discontinued treatment early will also be reported along with a tabulation of the reasons. Summary statistics for all participants on treatment arms will be reported e.g. median/mean time on treatment, these statistics will be tailored for the specific arms as naturally the treatments may widely differ and thus different summary measures will be relevant.

7 SAFETY ANALYSIS

The number of serious adverse events (including SARs and SUSUARs), and the number of treatment-related deaths will be reported for each treatment arm. The reporting period for Adverse Events/Serious Adverse Events (SAE's) will commence from the date of consent. Safety will be assessed by looking at adverse events (CTCAE).

The following details will be reported for each treatment arm for all patients who are part of the safety population:

- Adverse events at baseline, summarised by event and number of patients experiencing such events.
- Max grade experienced for all patients.
- A summary of number of events and patients for all toxicities by event and grade.
- The number of events and patients for all grades of toxicities.
- All serious adverse events will be reported, details to be presented include but are not limited to; admitting event, other events, reason for SAE, outcome, sequel and relatedness.

8 ANALYSIS

For all analyses data will be analysed for each intervention against the control group, including in each analysis only those participants who were eligible for the those treatment arms at the point of randomisation. The primary analysis will be conducted on the MITT population and all secondary analyses will be conducted on both the MITT population and ITT unless otherwise specified.

New intervention arms may be added as new interventions become available. All comparisons will be performed temporally with regards to control arm data.

8.1 Analysis of Primary Outcome Measure

The CRP data will be modelled using Bayesian multi-level models that allow for nesting of the repeated measures data within patient, and allowing for non-linear responses. This approach will facilitate an assessment of the effects of the treatments on the CRP. Specifically, posterior probabilities for the treatment/time interaction term will be used to conduct decision making. Care status as a randomisation stratification factor will be incorporated accordingly into the model structure along with age as a known prognostic indicator.

At the specified decision points, with interim analyses at n=20 and n=40 and a final analysis at n=60 per arm, the CRP data will be considered in the context of the emerging safety data to make a recommendation as outlined below:

a) If there is strong evidence of an additional anti-inflammatory effect (CRP) and a satisfactory safety profile consider progression to clinical endpoint evaluation whether in this trial or in another one

b) Terminate arm and do not proceed (based on lack of evidence of an additional biological effect or of an unfavourable safety signal)

We will define that 'strong evidence' or 'success' will be if there is an 90% probability that the intervention arm is better than usual care in reducing CRP as seen by the treatment/time interaction covariate. 'lack of evidence' or 'futility' is defined as less than 50% probability of the intervention being better than usual care. However, given the large number of agents being investigated in various phase II trials, the size of effect and the totality of data will be reviewed before recommending adoption by a phase III platform.

In addition to the above analysis we will analyse the data using two further approaches, namely, modelling AUC and an additional joint-modelling approach for CRP and discharge/death, this is to ascertain if censoring events for CRP; discharge/death, have had any impact on inference and if so to model accordingly.

8.2 Analysis for Secondary Outcome Measures

Outcome measures

- World Health Organisation (WHO) Clinical Progression improvement Scale
  - Time to improvement, measured from the date of randomisation, an event here is defined as at least a one-point improvement on the Time to Clinical Improvement Scale. A Kaplan-Meier plot will be produced for each treatment and control arm comparison, estimates of median time to improvement will be reported along with associated confidence intervals (where they can be estimated). In addition to the one-point improvement an additional analysis utilising a two-point improvement will be conducted, to be comparable with other studies.
  - Patients' scores on the Clinical Improvement Scale for each day will be displayed graphically, and modelled using Bayesian longitudinal ordinal regression, as described by Harrell (`http://hbiostat.org/proj/covid19/bayesplan.html`).
- The ratio of the oxygen saturation to fractional inspired oxygen concentration (SpO2/FiO2) will be presented graphically over time.
- Length of hospital stay will be summarised via descriptive statistics, stratified by treatment group. Reasons for such lengths of stay will be reported and summarised accordingly.
- Respiratory rate, body temperature and NEWS-2, will be plotted over time and summarised through descriptive statistics. These measures may also be modelled over time using multilevel modelling. Exploratory data analysis will drive model formulation, assumptions will be tested accordingly. All modelling will be exploratory in nature.
- The proportion of patients discharged at day 28 along with destination of discharge will be presented accordingly.
- Hospital survival status at 28 days will be reported as a tabulation of the proportion of patients who have died, been discharged or are still in hospital by day 28. Hospital-free days will be summarised through descriptive statistics, patients still in hospital or who have died will be incorporated having 0 hospital-free days.

- Lymphocyte, neutrophil and full blood counts with lymphocyte: neutrophil ratios and ferritin, D-Dimer and Triglycerides LDH values will be plotted over time and summarised through descriptive statistics. These measures may also be modelled over time using multilevel modelling. Exploratory data analysis will drive model formulation, assumptions will be tested accordingly. All modelling will be exploratory in nature.
- AEs and SAEs will be analysed as per section 7
- Overall Survival - Measured from the date of registration, an event here is defined as death. Patients are followed up until they have either died or are censored at date last seen. A Kaplan-Meier plot will be produced for each comparison, estimates of median survival will be reported along with associated confidence intervals (where they can be estimated)

8.3 Subgroup Analysis

Exploratory subgroup analyses will be conducted to attempt to ascertain the effect of disease severity on outcomes. The subgroups of 'non-severe disease' and 'severe disease' are defined as those that have a baseline WHO score of < 6 and ≥ 6 respectively. Other exploratory subgroup analyses may be conducted based on known prognostic indicators e.g. age group.

9 SAMPLE SIZE

The tables below demonstrate the operating characteristics of a trial design with the chosen decision criteria, based on a simpler analysis of area under the curve for sequential CRP data, with effect sizes informed from a dataset from 1026 hospitalised COVID-19 patients at Queen Elizabeth Hospital, Birmingham.

It is anticipated that our proposed hierarchical analysis will have superior operating characteristics. In our simulations, we compared a traditional fixed trial design recruiting 120 patients with candidate adaptive designs. We present basic operating characteristics for the fixed design (Table 1) and the chosen adaptive design (Table 2). We studied six scenarios of treatment effect, and estimated, through simulation, the probability of a trial stopping early for "success" or "fultility," and ultimately concluding success. Scenarios A, B, and C are beneficial effects of the intervention with (true) treatment effects of 0.25, 0.5 and 0.75 standard deviations, "null" is zero treatment effect and D and E are harmful effects of 0.25 and 0.5 standard deviations. "success" and "futility" are defined as above.

Table 1: Operating characteristics for a fixed trial design of 120 patients

Scenario	Probability stopping early for success	Probability stopping early for futility	Overall probability of success	Mean number of patients
Null	0	0	0.101	120
A	0	0	0.537	120
B	0	0	0.926	120
C	0	0	0.997	120
D	0	0	0.008	120
E	0	0	0	120

The adaptive design achieves similar probabilities of success in scenarios where the treatment effect is truly beneficial (A, B and C), and increases the probability of success only slightly if the intervention is harmful (D and E). There is some increase in the probability of success if the treatment effect is zero (Type I error) but this is offset by the very substantial reducitions in the numbers of patients needed in all scenarios. Moreover, Type I error is not seen as a serious problem as all interventions would be evaluated further in Phase 3 trials.

Table 2: operating characteristics for an adaptive design with interim analyses at 40 and 80 patients

Scenario	Probability stopping early for success	Probability stopping early for futility	Overall probability of success	Mean number of patients
Null	0.140	0.607	0.143	70
A	0.471	0.254	0.573	74
B	0.847	0.062	0.910	61
C	0.974	0.010	0.989	51
D	0.030	0.918	0.031	54
E	0.003	0.985	0.003	47

10 STATISTICAL SOFTWARE

Statistical analyses will be carried out using relevant statistical software; SAS , Stata or R respectively. Version numbers and session details will be stated and logged with any analysis.

11 STORAGE AND ARCHIVING

Catalyst files are stored in a restricted access directory on a secure server and will be saved for archive purposes according to CRCTU policy and procedure.