CLINICAL STUDY REPORT

Optimized TacrolimuS and MMF for HLA Antibodies after Renal Transplantation: – 'OuTSMART'

A randomized controlled clinical trial to determine if a combined screening /treatment programme can prevent premature failure of renal transplants due to chronic rejection in patients with HLA antibodies.

Sponsor Protocol Code:	Version 14.0 08/07/2020
EudraCT Number:	2012-004308-36
ClinicalTrials.gov Identifier:	NA
REC Number:	12/L0/1759
Investigational Drugs (IMPs):	Tacrolimus, Mycophenolate Mofetil, Prednisolone
Indication:	Development of HLA antibodies
Development Phase:	Phase IV
Study Begin (FPFV):	FPFV: 11/09/2013
Study End (LPLV):	Primary EP data collection 29/11/2020
Report Version & Issue Date:	
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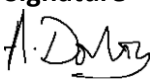
Chief Investigator:	Anthony Dorling

SIGNATURE PAGE

By signing below I approve the contents of this Clinical Study Report, and confirm that to the best of my knowledge it accurately describes the conduct and results of the study. The clinical trial reported herein was conducted in accordance with the principles contained in the Declaration of Helsinki, Good Clinical Practice (GCP) and all applicable laws and regulations.

Chief Investigator:

Printed name	**Signature**	**Date**
Anthony Dorling		21/12/21

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APPENDICES

1. Ethics

Independent Ethics Committee or Institutional Review Board
The study protocol and amendments were reviewed and approved by a National Research Ethics Service (NRES Committee London -Hampstead, Skipton House, Ground Floor, NRES/HRA, 80 London Road, London SE1 6LH)

Ethical conduct of the study
The trial was conducted according to the protocol and in compliance with the principles of the Declaration of Helsinki (1996) as amended, the principles of Good Clinical Practice (GCP) and in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, the Research Governance Framework for Health and Social Care, the Data Protection Act 1998 and other regulatory requirements as appropriate. The trial protocol and substantial amendments were reviewed by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA)

Subject information and consent
The local transplant clinic database was used to identify patients meeting the baseline inclusion / exclusion criteria. At the start of the trial, the entire population of transplant clinic attendees who met the eligibility criteria were potentially eligible for recruitment. On subsequent screening rounds, patients who reached 12 months post-transplantation after the start of the trial became eligible for recruitment before the next screening round.
Potentially eligible patients were approached at a routine clinic appointment by the PI or research nurses and given printed and verbal information about the trial. They had the opportunity to return for a second consultation within a few days to give informed consent for recruitment into the study or to do this on their next routine appointment. Alternatively, some eligible patients were sent information about the study through the post, for discussion and consent at their next routine appointment. Following consent, full eligibility criteria were reviewed. This included testing for chronic viral diseases (if no such test had been done within the last 5 years) or pregnancy (if history suggested the possibility of pregnancy).

2. Data Monitoring

An independent Trial Steering Committee (TSC) was convened in the post-award period. The membership was approved by the NIHR. The chair was Professor Chris Watson, from Cambridge. Other members were the CI (Professor Dorling), Professor Sunil Bhandari, Nephrologist form Hull, Mr Paul Newton, patient representative of the GSTT Kidney Patients Association, and Dr Craig Taylor, senior HLA clinical scientist from Cambridge. Members of the trial study team including the statistician and trial manager were also invited to attend. The TSC met 14 times during the study, up until the week before the COVID-19 pandemic began in March 2020. The Trial Manager prepared reports for the TSC and maintained minutes of all the meetings.
A Data Monitoring and Ethics Committee (DMC) was also established, and the membership agreed by the NIHR. The committee was chaired by Dr Nick Torpey, a Nephrologist from Cambridge. Other members included Dr Alan Wong, trials Pharmacist, Dr Issy Reading, independent statistician, and Dr Vaughan Carter, senior HLA clinical scientist. The DMC met 11 times during the study. The Trial Statistician prepared reports for the DMC and the trial manager maintained minutes of all the meetings.

3. Sponsors, Investigators and Trial Sites

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5. Study Synopsis

Title of clinical trial	A randomized controlled clinical trial to determine if a combined screening /treatment programme can prevent premature failure of renal transplants due to chronic rejection in patients with HLA antibodies.
Protocol Short Title/Acronym	Optimized TacrolimuS and MMF for HLA Antibodies after Renal Transplantation /OuTSMART
Study Phase	Phase IV
Sponsor name	King's College London / GSTT NHS Foundation Trust
Chief Investigator	Prof. Anthony Dorling
Eudract number	2012-004308-36
REC number	12/LO/1759
IRAS project ID:	112232
Medical condition or disease under investigation	Premature allograft failure / Chronic rejection
Purpose of clinical trial	The overall objective is to test whether a structured screening programme to identify patients with a validated prognostic biomarker for kidney transplant failure, allied with an optimized immunosuppression treatment protocol, can reduce the time to graft failure at the primary endpoint (approximately 43 months post-randomisation).
Primary objective	Compare the time to graft failure in patients with HLA Ab who receive an optimized anti-rejection medication intervention ('treatment'), with that in a control group with HLA Ab who remain on their established immunotherapy and whose clinicians are not aware of their Ab status.
Secondary objective (s)	a) Determine the time to graft failure in patients randomized to 'unblinded' HLA Ab screening, compared to a control group randomized to 'blinded' HLA Ab screening. b) Determine whether treatment influences patient survival

	c) Determine whether 'treatment' influences the development of graft dysfunction as assessed by presence of proteinuria (Protein:Creatinine Ratio > 50 or Albumin:Creatinine Ratio > 35) and change in estimated Glomerular Filtration Rate (eGFR). d) Determine whether 'treatment' influences the rates of acute rejection in these groups e) Determine the adverse effect profiles of 'treatment' in this group, in particular whether they are associated with increased risk of infection, malignancy or DM. f) Determine the cost effectiveness of routine screening for HLA Ab and prolonging transplant survival using this screening/treatment protocol. g) Determine the impact of biomarker screening and "treatment" on the patients' adherence to drug therapy and their perceptions of risk to the health of the transplant.
Trial Design	A prospective, open labelled, randomised marker-based strategy (hybrid) trial design, with two arms stratified by biomarker (HLA Ab) status. Recruitment will take place in 13 renal transplant units, recruiting for minimum of 45 months with recruits followed up intensively for 32 months (maximum 64 months) and primary endpoint assessed by remote evaluation when 43 months post-randomisation is ideally achieved by all.
Endpoints	Primary: Time to graft failure in HLA Ab positive patients randomized to biomarker-led treatment groups vs. time to graft failure in HLA Ab positive patients randomized to the control (standard care) group. Graft failure will be defined as re-starting dialysis or requiring a new transplant. Secondary: Clinical:

	• time to graft failure in patients randomized to unblinded HLA Ab screening vs. blinded screening • patient survival. • graft dysfunction, as assessed by two separate measures; presence of proteinuria (Protein:Creatinine Ratio > 50 or Albumin:Creatinine Ratio > 35) and change in estimated Glomerular Filtration Rates over 32 months. • rates of biopsy-proven T cell-mediated or antibody-mediated rejection over 32 months. • rates of culture-positive infection, biopsy-proven malignancy and diabetes mellitus. • health economic analysis of outcomes in intervention vs. control groups. • analysis of adherence and perceptions of risk in biomarker led care vs standard care groups.
Planned number of subjects	It is anticipated that approximately 2357 total patients will need to be recruited. Given the observed proportions of DSA participants, predicted drop outs and HLA Ab conversion rates, this will allow the target of 165 (~83 per group) DSA participants to be recruited. It is expected based on observed proportions, that this will result in approximately 824 (412 per group) non-DSA participants being recruited and 1368 (684 per group) participants remaining HLA Ab negative at the primary endpoint, exceeding the target numbers required for these groups.
Summary of eligibility criteria	Included: Renal transplant recipients aged 18-75, > 1 year post-transplantation, with estimated glomerular filtration rate (GFR) ≥30 by 4 variable MDRD. Excluded: Recipients of cross-match positive transplant requiring HLA desensitization to remove antibody, recipients of additional solid organ transplants (e.g. pancreas, heart etc), history of malignancy (with exclusions), recent acute rejection, recipients with hepatitis B, C or HIV, recipients known to

	have HLA antibody who have received specific treatment, known hypersensitivity to any of the IMPs, known hereditary disorders of carbohydrate metabolism, pregnancy, females who refuse to consent to using suitable contraception through trial, patients enrolled in any other studies involving administration of another IMP at time of recruitment.
IMP, dosage and route of administration	Oral Tacrolimus od or bd titrated to pre-dose levels of 4-8ng/ml. Oral Mycophenolate Mofetil or enteric coated mycophenolic acid bd, tds or qds given at highest tolerated daily dose or according to unit guidelines, with maximum dose determined by SmPC. Oral Prednisone od according to the following regime: 20mg od for 2 weeks tapering to 5mg od over 4 weeks.
Active comparator product(s)	None
Maximum duration of treatment of a subject	HLA Ab-screening phase will last 45 months. For each recruit, the duration of study will be a minimum of 32 months and up to 64 months, as patients who initially tested negative for HLA Ab, but become HLA Ab positive in the final screening round will be followed up for a further 32 months from that point.
Version and date of protocol amendments	Version14 08/07/2020 Version 13 21/11/18 Version 12 1/12/16 Version 11 26/11/2015 Version 10 11/08/2015 Version 9 15/10/2014 Version 8 1/7/2014 Version 7 7/4/2014 Version 6 6/12/2013 Version 5 9/7/2013 Version 4 13/5/2013 Version 3 29/1/2013 Version 2 07/11/12 Version 1 04/10/12

6. Glossary of terms

Adverse event (AE)
Albumin creatinine ratio (ACR)
Antibody (Ab)
Biomarker Led Care (BLC)
Chronic antibody-mediated Rejection
Confidence interval (CI)
Coronavirus Disease (COVID-19)
Data Monitoring and Ethics Committee (DMC)
Diabetes Mellitus (DM)
Donor specific antibody (DSA)
Glomerular Filtration Rate (eGFR)
Good Clinical Practice (GCP)
Hepatitis B surface antigen (HBSAg)
Hepatitis C (HepC)
Human Immunodeficiency Virus (HIV)
Human Leukocyte Antigen (HLA)
Intention to treat (ITT)
Interquartile range (IQR)
Investigational Medical Product (IMP)
Medicines and Healthcare products Regulatory Agency (MHRA)
Modification of diet in Renal disease (MDRD)
Mycophenolate Mofetil (MMF)
Negative (Neg)
Non-donor specific antibody (NDSA)
Potassium (K+)
Protein Creatinine ratio (PCR)
Quality adjusted life years (QALY)
Serious adverse event (SAE)
Serious adverse reaction (SAR)
Severe Unsuspected serious adverse reaction (SUSAR
Sodium (Na+)
Standard Care (SC)
Stanndard deviation (SD)
Statistical Analysis Plan (SAP)
Summary of product characteristics (SMPC)
Tacrolimus (Tac)
Timepoint (T)
Trial Steering Committee (TSC)

7. Publication (reference)

Dorling A, Rebollo-Mesa I, Hilton R, Peacock JL, Vaughan R, Gardner L, Danzi G, Baker R, Clark B, Thuraisingham RC, Buckland M, Picton M, Martin S, Borrows R, Briggs D, Horne R, McCrone P, Kelly J, Murphy C. "Can a combined screening /treatment programme prevent premature failure of renal transplants due to chronic rejection in patients with HLA antibodies: Study protocol for the multicentre randomised controlled OuTSMART trial." Trials. 2014 Jan 21;15(1):30. DOI: 10.1186/1745-6215-15-30. PMID: 24447519: WOS:000333465400002

Stringer D, Goldsmith K, Peacock JL, Gardner LM, Murphy C, Dorling A. Sample size adaptations in a randomised controlled biomarker based strategy (hybrid) trial: experience from the OUTSMART trial. Trials 2017;18. WOS:000410814200056.

Stringer D, Gardner LM, Peacock JL, Rebollo-Mesa I, Hilton R, Shaw O, Baker R, Clark B, Thuraisingham RC, Buckland M, Picton M, Worthington J, Borrows R, Briggs D, Shah S, Shiu KY, McCullough K, Phanish M, Hegarty J, Stoves J, Ahmed A, Ayub W, Horne R, McCrone P, Kelly J, Murphy C, **Dorling A**. Update to the study protocol, including statistical analysis plan for the multicentre randomised controlled OuTSMART trial: a combined screening/treatment programme to prevent premature failure of renal transplants due to chronic rejection in patients with HLA antibodies. Trials 2019 Aug 5;20(1):476. doi: 10.1186/s13063-019-3602-2. PMID: 31383029

Clarke AL, Ghanouni A, Gardner LM, Dorling A, Horne R. Do kidney transplant recipients perceive corticosteroids more negatively than other immunosuppressants? Int J Clin Pharm-Net 2021;43(1):290-290. WOS:000617206400046..

Ghanouni, A. Clarke, A. Bidad, N.Gardner, L.M. Hilton, R. Picton, M. Thuraisingham, R. Borrows, R. Baker, R. McCullogh, K. Stoves, J. Phanish, M. Shah, S. Shiu, K.Y. Ahmed, A. Ayub, W. Hegarty, J. Dorling, A. Horne, R. Analysis of baseline treatment necessity beliefs, concerns, and adherence in questionnaires from 1,598 kidney transplant recipients enrolled in the OuTSMART trial reveals highly positive ratings for immunosuppressive drugs apart from corticosteroids. 2021 Submitted.

8. Study period (years)

The first patient First Visit was 11/09/2013. The end of the trial was defined as the point at which all of the remote collection of the primary endpoint data was achieved. This was 29/11/2020.
Patient recruitment finished on 27/10/2016 (the last participant was consented on 27/10/2016 and randomised on 4th November 2016)
The trial was temporarily suspended during the first COVID-19 pandemic (20/03/2020 – 01/09/2020), and date for completion of primary endpoint data collection extended from June 2020 to November 2020. The trial was not terminated prematurely.

9. Phase of development

Phase IV

10. Objectives

The overall objective is to test whether a structured screening programme to identify patients with a validated prognostic biomarker for kidney transplant failure, allied with an optimized immunosuppression treatment protocol, can reduce transplant failure rates over time.

Primary objective;
Determine the time to graft failure in patients testing positive for HLA Ab at baseline or within 32 months of randomization who receive an optimized anti-rejection medication intervention with prednisone, Tac and MMF ('treatment'), compared to a control group who test positive for HLA Ab at baseline or within 32 months post-randomization who remain on their established immunotherapy and whose clinicians are not aware of their Ab status. The primary endpoint will be assessed remotely when 43 months post-randomisation has ideally been achieved by all.

Secondary objectives;
a) Determine the time to graft failure in patients randomized to 'unblinded' HLA Ab screening, compared to a control group randomized to 'blinded' HLA Ab screening.
b) Determine whether 'treatment' influences patient survival
c) Determine whether 'treatment' influences the development of graft dysfunction as assessed by presence of proteinuria (Protein:Creatinine Ratio > 50 or Albumin:Creatinine Ratio > 35) and change in estimated Glomerular Filtration Rate (eGFR).
d) Determine whether 'treatment' influences the rates of acute rejection in these groups
e) Determine the adverse effect profiles of 'treatment' in this group, in particular whether they are associated with increased risk of infection, malignancy or DM.
f) Determine the cost effectiveness of routine screening for HLA Ab and prolonging transplant survival using this screening/treatment protocol.
g) Determine the impact of biomarker screening and "treatment" on the patients' adherence to drug therapy and their perceptions of risk to the health of the transplant.

11. Background and Context

Kidney transplantation is the gold standard treatment for end stage renal failure, but kidney transplants do not last for the natural lifespan of most recipients. Current death-censored 10-year transplant survival rates vary between 59 and 70%, so 30-40% of patients have their transplant for < 10 years and around 3% of prevalent kidney transplants fail annually, meaning that thousands of patients worldwide return to dialysis each year. Although many of these patients are eligible for a second transplant, the legacy of the first often makes it harder to find a well-matched second kidney. In addition, second (and any subsequent) transplants have a shorter lifespan than the original transplant, so the problem of premature failure becomes amplified. Of the various reasons why transplanted kidneys fail, the single biggest

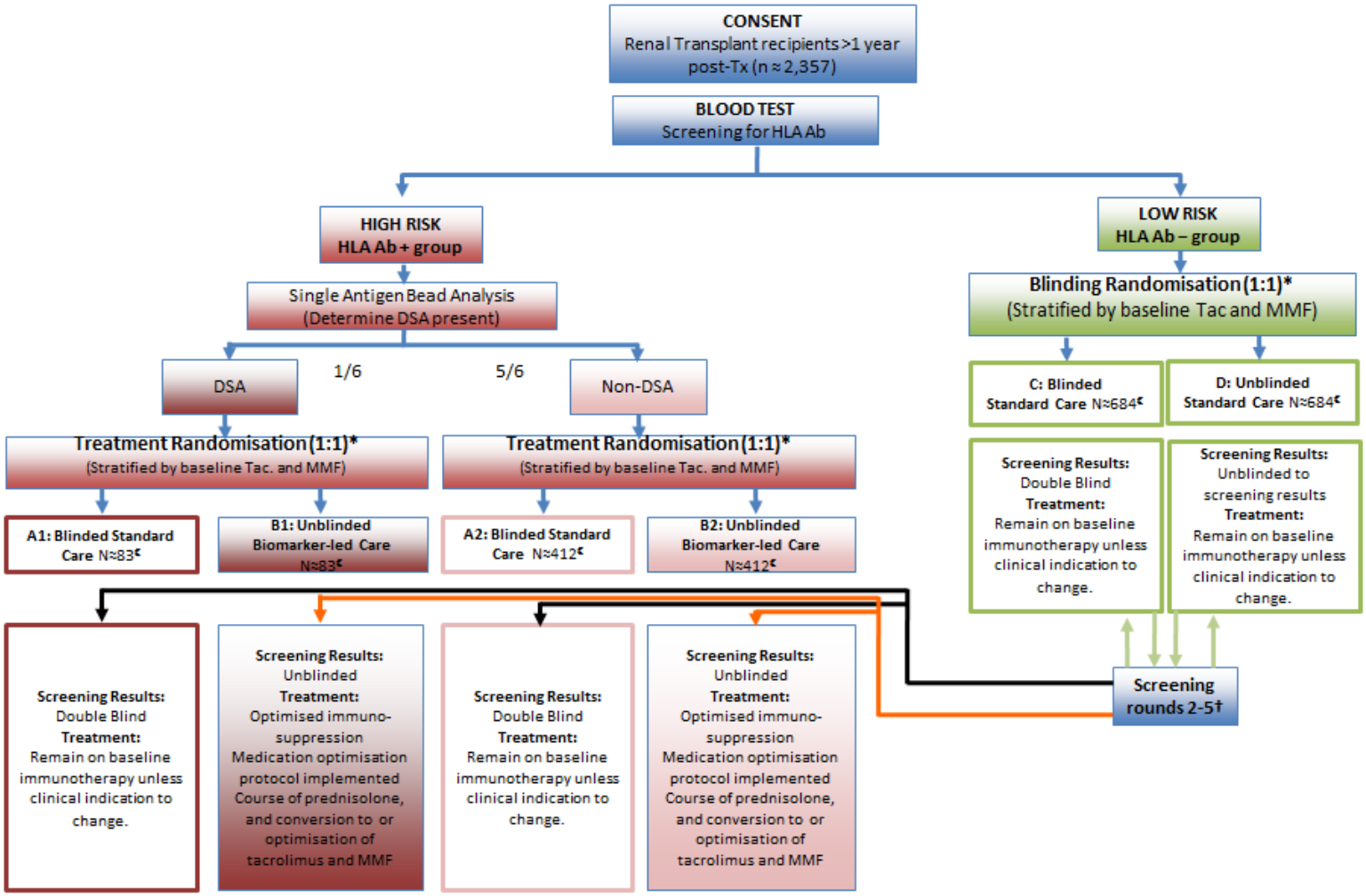
cause is immune-mediated injury, primarily directed against mismatched donor human leukocyte antigens (HLA).
The appearance of circulating antibodies (Ab) against HLA has been validated as a strong prognostic biomarker of kidney transplant failure by case control and prospective observational studies. Development of HLA Ab is associated with a >3x greater risk of graft failure, even after correction for other risk factors associated with graft loss and is often followed by a period of progressive graft dysfunction prior to failure, though the rate of deterioration in individual patients is highly variable. Moreover, the presence of HLA Ab specific for the kidney donor HLA (donor specific antibodies – DSA), found in approximately 33% of HLA Ab positive patients carry a higher risk of graft loss compared to those that are not donor-specific (non-DSA, found in approximately 66%).
Although the HLA Ab themselves might be involved in pathological damage to the graft , other effector mechanisms could be operating, as HLA Ab production is dependent on activation of multiple components of the recipient immune system, including donor-specific T and B lymphocytes. Our previous work in kidney transplant recipients showed a strong correlation between the activity of anti-donor CD4+ T and B lymphocytes and the rate of deterioration in graft function in patients with evidence of Ab-mediated pathology. Consistent with the work of others, we also showed that optimised treatment with tacrolimus and mycophenolate mofetil acted to stabilise graft function, and correlated this with suppression of interferon$-\gamma$ production by anti-donor T cells, independently of any changes in the circulating Ab. This suggested that the functional activity of cellular components of the anti-donor response was relevant to the rate of graft deterioration that preceded graft failure. This work, along with data linking poor compliance with immunosuppression drugs to chronic allograft dysfunction, established the foundation for the OuTSMART study, in which we tested the hypothesis that routine surveillance for the development of HLA Ab, combined with optimised 'treatment' in those who became HLA Ab+, would prevent the premature failure of transplanted kidney allografts .

12. Methodology

Prospective, open labelled, randomised marker-based strategy (hybrid) trial design, with two arms stratified by biomarker (HLA Ab) status. Recruitment will take place in 13 renal transplant units, recruiting for 45 months with recruits followed up intensively for at least 32 months (maximum 64 months) and primary endpoint assessed by remote evaluation after 43 months post-randomisation is ideally achieved by all. The trial design is represented in the flow diagram in section 2.3, showing the number of patients anticipated to be in each group by the end of the trial, based on sample size calculations, consent rates, eligibility and estimated fall-out. Using the flow diagram (top-to-bottom) as a guide: recipients of cross-match negative transplants aged 18-75, > 1 year post-transplant with an eGFR ≥ 30 will consent to the screening/treatment process. The first stratification will result from blood test screening for HLA Ab. Approximately 35% will be HLA positive, with ~65% negative. The HLA Ab+ patients will be further screened with single antigen beads to determine whether DSA are present (~1/6 DSA and 5/6 non-DSA). Thus, biomarker stratification leads to three groups (DSA+, non-DSA+ and HLA Ab-neg). The second stratification will be based on current immunosuppression, to ensure balanced numbers already on Tac or MMF in each group. The final stratification will be by site. HLA Ab positive patients will be randomized 1:1 into either Blinded Standard Care or Unblinded Biomarker led-care. Patients in the former (groups A1 &

A2 in the flow chart in 2.3) will be blind to their biomarker status and will remain on baseline immunotherapy, whereas patients in the latter (groups B1 and B2 in the flow chart) will know their HLA Ab status and will be offered “treatment”. HLA Ab-negative patients will remain on their existing immunotherapy and randomized 1:1 into either Blinded (group C) or Unblinded groups (D), with only the latter knowing their HLA Ab status. Both these groups will receive regular Ab status monitoring for the first 3 years. Those patients who become positive during subsequent screening rounds (~10% per year) will be moved to the appropriate HLA Ab positive groups (DSA+ or non-DSA+) for final data analysis. All patients in group D found to be positive on second or subsequent rounds will be offered the same “treatment” as those patients who were positive in the first screening round, and be intensively followed up for an additional 32 months from the time they become positive. Thus the maximum amount of time any single patient may remain in intensive follow up is 64 months. New patients will be recruited to the study at each successive screening round.

Trial Flowchart



*Randomisation performed on results of a recruit's first screening test. Those with HLA Ab undergo no further screening as part of the trial (but serum will be stored for analysis of HLA Ab profiles later). †Those initially HLA Ab-negative undergo routine screening every 8 months. THERE IS NO SECOND RANDOMIZATION: If a recruit allocated to Blinded standard care (group C) becomes HLA Ab positive (black lines), he/she remains in Standard care group (group A1 or A2). If in unblinded standard care group (D), they change to unblinded biomarker-led treatment care (group B1 or B2) (orange lines). € Numbers in each group are those anticipated at the end of study.

Table : Schedule of events

Phase	Peri-Randomization	Post-Randomization											
		Unblinded HLA Ab+ groups – Approximate times of assessment (+/- 1 week). Once stabilised, go to month 8 assessment						All Groups – Approximate times of assessment (+/- 3 months)					
Study Week/month	Day -56 to 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Month 8	Month 16	Month 24	Month 32	Min 43 months	Month 90-92
Informed consent	x												
Inclusion/Exclusion Criteria	x[1]												
Medical History inc. Drugs	x[2]												
Transplant / sensitisation Hx	x												
Registration / Demographics	x[3]												
Weight / BP	x							x	x	x	x		
Urine PCR or ACR	x							x	x	x	x		
Haematology[4]	x		X		x		x	x	x	x	x		

[1] Including virology and pregnancy testing where appropriate.
[2] For registration, need to know whether already on tacrolimus and / or MMF/Myfortic.
[3] Do this prior to taking blood for HLA Ab screening
[4] Hb, WCC, platelet count at all time periods

Biochemistry	x[5]		x[6]		x[8]		x[8]	x[7]	x[8]	x[9]	x[10]		
[Calcineurin inhibitor] trough	x	x[9]	X	x	x	x	x	x	x	x	x		
Total immunoglobulin (or IgG, IgM +/- IgA)	x								x		x		
HLA antibody screening	x[10]							x[12]	x[12]	x[12]	x[12]		
Apply optimized treatment protocol[11]		x	X	x	x	X	x						
See Trial-specific Nurse	x							x	x	x	x		
Record Medications	x							x	x	x	x		
Adverse Events Form		x	X	x	x	X	x	x	x	x	x		
Questionnaire for analysis of adherence / risk	x									x			
Questionnaire for health economics	x								x				
Primary Endpoint (remote data collection)												x	
Primary Endpoint (sensitivity analysis; remote data collection)													x

[5] Creatinine, Na^+, K^+, bicarbonate, calcium, CRP, lipid profile, glucose, HbA1c.
[6] Creatinine, Na^+, K^+, glucose, HbA1c
[7] Creatinine, Na^+, K^+, bicarbonate, calcium, CRP, glucose, HbA1c
[8] As enrolment biochemistry
[9] In those patients having optimization of tacrolimus – continue until trough levels achieved
[10] At enrollment, on everyone. Beyond enrollment, send sample from recruits in unblinded HLA Ab-negative group and ALL blinded patients.
[11] Ideally participant will see a physician once a month whilst being optimized. Visit details are recorded in an Optimisation Log and not in the eCRF.

Trial Medication
See below

13. Number of patients (planned and analysed)

13.1 Planned

The trial was originally expected to recruit for a minimum of 45 months. The target was originally to recruit 278 DSA + patients when the original endpoint was graft failure rates in 3 years. An estimated 2522 patients were needed to recruit this target. Following the realization that assumptions about rates of DSA positivity were low, and the change in the primary endpoint to time to graft failure, we changed the target DSA recruitment to 165 patients. This target included those HLA Ab negative participants who developed do-novo antibodies at the 8 monthly re-screening rounds and hence moved into the DSA+ group. We estimated recruiting this many DSA+ would involve recruiting and screening 2357 patients overall.

13.2 Analysed

Between September 2013 and October 2016, 5887 renal transplant recipients from 13 UK transplant centres were assessed for eligibility of which 2094 were enrolled (consented). The reasons for non-enrolment of the other 3850 patients are shown in figure 1 (CONSORT). 57 patients were found to be ineligible after post-consent checks, meaning 2037 were randomised after HLA antibody screening. Recruitment was halted when we reached the target of DSA+ patients, but because screening only finished once all HLA Ab-negative patients had been screened at least once, we ended up with a total of 198 DSA+ recruits.

Figure 1 - CONSORT diagram

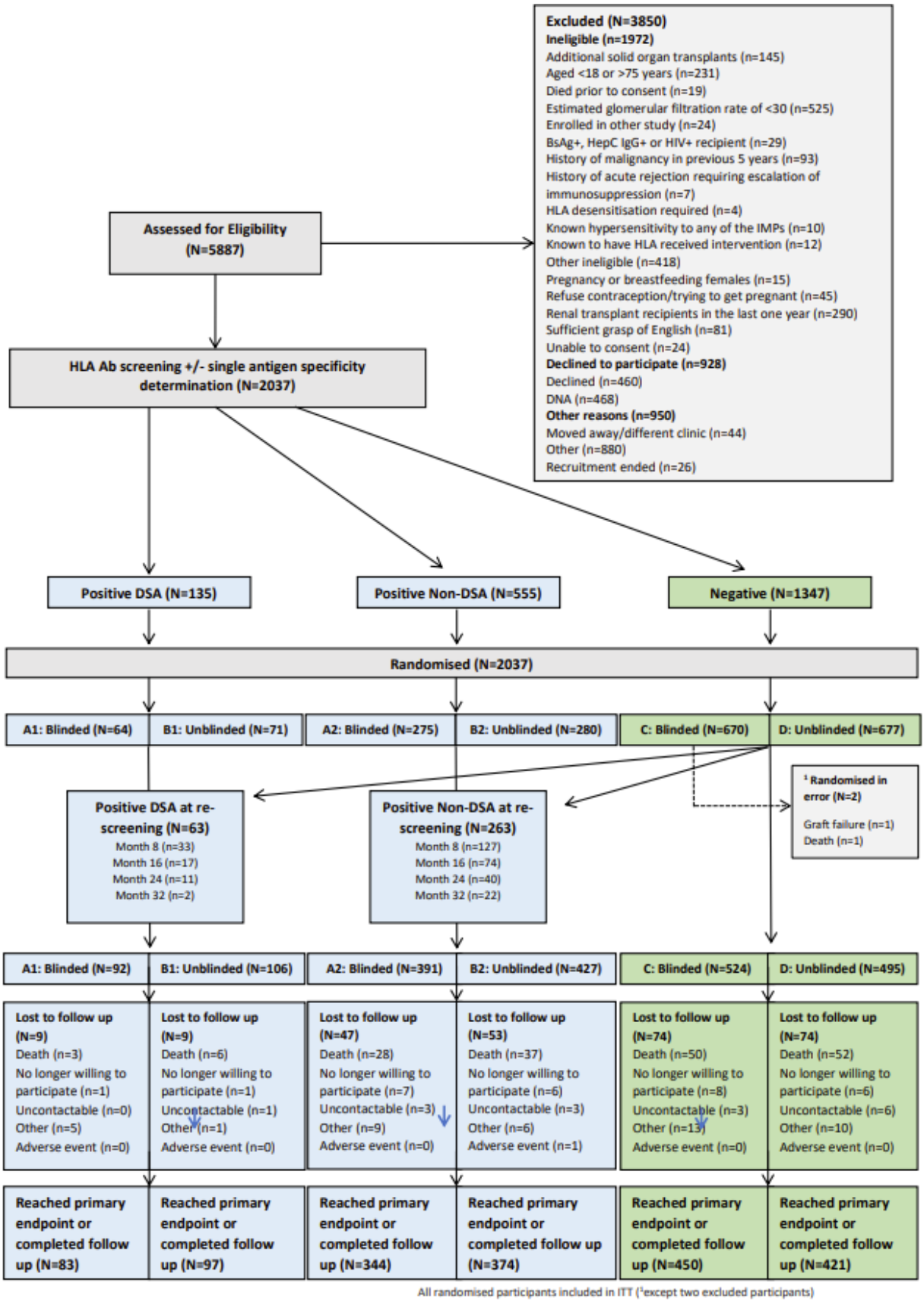


Table 1 - Reasons for patient withdrawal from the study by HLA group and Trial arm

Withdrawal category	DSA BLC	DSA SC	Non-DSA BLC	Non DSA SC	Neg Unblinded	Neg Blinded	Total
Adverse event	0 (-)	0 (-)	1 (6.2%)	0 (-)	0 (-)	0 (-)	1 (1.1%)
Participant no longer willing to participate for other reasons	1 (33%)	1 (17%)	6 (38%)	7 (37%)	6 (27%)	8 (32%)	29 (32%)
Unable to locate / contact participant	1 (33%)	0 (-)	3 (19%)	3 (16%)	6 (27%)	3 (12%)	16 (18%)
Other (see below)	1 (33%)	5 (83%)	6 (38%)	9 (47%)	10 (46%)	14 (56%)	45 (50%)

This table does not include death which is a secondary endpoint and so not considered withdrawal from the study (but were considered lost to further follow up).

Table 2 – Other reasons for withdrawal

Other Reason for Withdrawal	SC	BLC	Total
Care taken over at another hospital	0 (-)	1 (5.9%)	1 (2.2%)
Care transferred to another NHS Trust	1 (3.6%)	0 (-)	1 (2.2%)
Moved care to K & C.	1 (3.6%)	0 (-)	1 (2.2%)
Moved care to Norfolk & Norwich.	1 (3.6%)	0 (-)	1 (2.2%)
Non attendance at clinic	0 (-)	1 (5.9%)	1 (2.2%)
Partcipant should have not been randomised due to graft failure prior randomisation	1 (3.6%)	0 (-)	1 (2.2%)
participant care moved to another hospital not participating in OutSMART	1 (3.6%)	0 (-)	1 (2.2%)
Participant has moved to Wales and unable to contact him.	0 (-)	1 (5.9%)	1 (2.2%)
Participant moved to a hospital not involved in the OuTSMART trial	1 (3.6%)	0 (-)	1 (2.2%)
Participant moved to another hospital not involved in the OuTSMART trial	4 (14.3%)	1 (5.9%)	5 (11.1%)
Participant moved to another hospital not involved with the OuTSMART trial	1 (3.6%)	0 (-)	1 (2.2%)
Patient has left the country and no further data on EPR	0 (-)	1 (5.9%)	1 (2.2%)
Patient has moved to a trust not associated with the OuTSMART Trial	0 (-)	1 (5.9%)	1 (2.2%)
Patient has moved to a trust not taking part in OuTSMART	0 (-)	1 (5.9%)	1 (2.2%)
Patient moved care to Brighton.	1 (3.6%)	0 (-)	1 (2.2%)
Patient moved care to King's Hospital.	0 (-)	1 (5.9%)	1 (2.2%)
Patient moved care to Norfolk.	0 (-)	1 (5.9%)	1 (2.2%)
Patient moved care to Portsmouth.	1 (3.6%)	0 (-)	1 (2.2%)
Patient moved to a hospital not involved with the OuTSMART trial.	1 (3.6%)	0 (-)	1 (2.2%)
Patient moved to a trust not taking part in the OuTSMART trial	1 (3.6%)	0 (-)	1 (2.2%)
Patient moved to another hospital not involved with OuTSMART trial	1 (3.6%)	0 (-)	1 (2.2%)

Other Reason for Withdrawal	SC	BLC	Total
patient moved to another region (centre not participating in this study)	1 (3.6%)	0 (-)	1 (2.2%)
Patient moved to Singapore.	0 (-)	1 (5.9%)	1 (2.2%)
Patient moved to Zurich.	0 (-)	1 (5.9%)	1 (2.2%)
patient relocated to another hospital	3 (10.7%)	1 (5.9%)	4 (8.9%)
patient relocated to another hosptial	1 (3.6%)	0 (-)	1 (2.2%)
Patient transfered care to Brighton Hospital	0 (-)	1 (5.9%)	1 (2.2%)
patient transferred to Leeds where transplant was performed in 2009	1 (3.6%)	0 (-)	1 (2.2%)
patient transferred to other hospital not participating in OuTSMART	1 (3.6%)	0 (-)	1 (2.2%)
Patient under palliative care team at a different hospital, prognosis is poor. All appointments at U	1 (3.6%)	0 (-)	1 (2.2%)
Patient wishes to withdraw	0 (-)	1 (5.9%)	1 (2.2%)
Pt moved to Scotland	1 (3.6%)	0 (-)	1 (2.2%)
referral to another renal unit	1 (3.6%)	0 (-)	1 (2.2%)
Relocated and not contactable	1 (3.6%)	0 (-)	1 (2.2%)
relocated to Newcastle	0 (-)	1 (5.9%)	1 (2.2%)
transferred to another hospital	0 (-)	1 (5.9%)	1 (2.2%)
Transferred to Countess of Chester Hospital and we were advised to withdraw pt as no follow up there	1 (3.6%)	0 (-)	1 (2.2%)
transferred to Scotland	0 (-)	1 (5.9%)	1 (2.2%)

14. Diagnosis and main criteria for inclusion

Inclusion Criteria

• Sufficient grasp of English to enable written and witnessed informed consent to participate.
• Renal transplant recipients >1 year post-transplantation, male or female
• Aged 18-75 years
• Estimated glomerular filtration rate (eGFR by 4 variable MDRD) of ≥30 (within the previous 6 months of signing consent or taken at screening if not done in the previous 6 months).

Exclusion Criteria

• Recipient requiring HLA desensitisation to remove antibody for a positive XM transplant
• Recipient known already to have HLA antibody WHO HAS RECEIVED specific intervention for that antibody or for CAMR / chronic rejection
• Recipient of additional solid organ transplants (e.g. pancreas, heart, etc).
• History of malignancy in previous 5 years (excluding non-melanomatous tumours limited to skin)
• HBsAg+, HepC IgG+ or HIV+ recipient (on test performed within previous 5 years)
• History of acute rejection requiring escalation of immunosuppression in the 6 months prior to screening.
• Patient enrolled in any other studies involving administration of another IMP at time of recruitment

The following exclusion criteria are based on information contained within the SMPcs of the IMPs

• Known hypersensitivity to any of the IMPs
• Known hereditary disorders of carbohydrate metabolism
• Pregnancy or breastfeeding females (based on verbal history of recipient)

• Pre-menopausal females who refuse to consent to using suitable methods of contraception throughout the trial.

15. Test product, dose and mode of administration

Baseline therapy

All treatments were introduced on the basis that they will be tailored to the individual patient, according to compliance, tolerance and achievement of target levels (for Tac). Failure to tolerate one or more of the components of the protocol (or refusal to take any of the agents) was not be used as a reason for withdrawal from the study.

IMP

The 'optimized treatment' protocol in the two groups (B1, B2) with HLA Ab was (as defined in the protocol);

a) Mycophenolate mofetil bd, tds or qds, or enteric coated mycophenolic acid bd, with daily dose determined according to local unit guidelines. The patient will be stabilized on the maximum tolerated dose.

b) Tacrolimus od or bd, according to local unit preference, with dose titrated to achieve 12-hour post-dose levels of 4μg/L to 8μg/L (4-8 ng/ml). The patient will be stabilized on the maximum tolerated dose that achieves these levels.

c) Prednisolone od. Starting at 20mg for two weeks, then reducing by 5 mg od every two weeks down to their previous maintenance dose or 5mg od, if not previously taking.

After consultation with the MHRA, we confirmed that all these medicines will be classed as IMPs, whereas all others will not. Mycophenolate mofetil/mycophenolic acid is being used outside of its Marketing Authorisation (which states that it should be used with ciclosporin). However, because it is now used so widely in combination of tacrolimus in most units in the UK, the two can be regarded as 'standard care'. The three drugs did not require labelling in line with annex 13. This means the IMPs were managed in the same way as normal i.e. GP or hospital prescription (as appropriate) and did not require special labelling/accountability/storage etc.

Doses were tailored to each individual according to the protocol above. The mean (SD) and range of doses for each IMP administered in the B1 (HLA Positive DSA BLC) and B2 (HLA Positive Non-DSA BLC) groups are given below.

Table 3 - Mean IMP doses prescribed

Trial Arm/HLA status at rescreen	N	Mean (SD)	Range
Tacrolimus (mg)			
DSA BLC (B1)	86	5.2 (3.7)	1-18
Non-DSA BLC (B2)	355	5.2 (3.7)	1-24
MMF (mg)			
DSA BLC (B1)	77	1237(450)	500-2000
Non-DSA BLC (B2)	305	1149 (456)	250-2000
Prednisolone (mg)			
DSA BLC (B1)	80	5.3 (2.1)	2-20
Non-DSA BLC (B2)	267	5.2 (1.8)	1-25

16. Duration of treatment

Following recruitment to the trial, all patients had 32 months of intensive follow up involving 8-monthly clinic visits post-randomisation, except in the following scenario; patients in groups C or D who became Ab positive during the initial 32 months follow up were transferred to the relevant Ab+ group and underwent intensive follow up for a further 32 months from date of transfer. This was to ensure that all newly positive patients, picked up by the screening, had a minimum of 32 months intensive follow-up. Therefore, the maximum amount of time that any single patient remained in intensive follow up was 64 months. The secondary endpoints will be assessed at the end of the intensive follow up period (32 months up to 64 months) and at this point trial procedures relating to the participants will finish. The participants will be informed that they no longer are required to attend research clinic visits.

The last participant research clinic visit was expected to be in March 2020 with the assessment of the primary endpoint being performed during the final three months of the trial concluding at the end of June 2020 when the last participant recruited reached 43 months post-randomisation. However, due to the coronavirus pandemic in the UK in 2020 most clinical trial activity, including this trial, was severely limited and so it was not possible to rely on the original plan to obtain the primary endpoint data between April and June 2020. For this reason, the best alternative was to obtain the primary endpoint data from patients' clinic notes. Evidence for graft failure or death was taken from the participants' last hospital contact prior to March 16th, 2020. These data, which reflect participants' pre-COVID status, were used for the primary endpoint analysis. Evidence of graft failure or death was also taken from participants' notes from their most recent hospital contact at the point of a final assessment between September 1 2020 and November 30 2020. During this designated three-month window, endpoint data was collected from each patients' notes only once. These data, reflecting status post-onset of COVID crisis, were used for a sensitivity analysis. The trial concluded by November 30 2020. The end of trial for this study has been defined as the last follow up of primary outcome data.

17. Reference therapy, dose and mode of administration

Patients in all groups had blood pressure controlled and total cholesterol lowered, using agents according to local unit guidelines and working to unit-defined targets. All other medication and treatment were determined by local unit guidelines.

18. Criteria for evaluation: Endpoints

18.1 Efficacy

Primary end-point

The primary endpoint is time to graft failure in HLA Ab positive patients randomized to biomarker led care groups vs. time to graft failure in HLA Ab + patients randomized to standard care groups assessed at 43 months post-randomisation achieved ideally by all. Graft failure will be defined as re-starting dialysis or requiring a new transplant.

Secondary Efficacy Parameters

The secondary clinical endpoints are:

• time to graft failure in patients randomized to blinded HLA Ab screening vs those randomized to unblinded screening. Graft failure will be defined as re-starting dialysis or requiring a new transplant.

The following endpoints will be assessed at end of intensive follow up (32 months):

• graft dysfunction, as assessed by two separate measures proteinuria (Protein:Creatinine Ratio > 50 or Albumin:Creatinine Ratio > 35) and change in estimated Glomerular Filtration Rates, and the rate of progression to graft dysfunction.

• rates of biopsy-proven rejection.

• health economic analysis of outcomes in intervention vs. control groups.

• analysis of adherence and perceptions of risk in BLC groups.

18.2 Safety

Safety Parameters

The trial was deemed a type A trial by the MHRA. The final criteria for reporting Serious adverse events to the sponsor were:

AEs in those in whom medication was assigned IMP status (i.e. those in the unblinded HLA Ab positive arm who underwent optimization) that fulfil the following criteria will be reported to the sponsor and MHRA:

a) result in death

b) require hospitalisations resulting in kidney graft failure

c) are SAR's that would prompt yellow-card reporting in the blinded arm of the trial.

All other AEs were recorded in the Case Report forms but were not reported to the sponsor

Specific Safety Endpoints

• patient survival.

• rates of culture- or polymerase chain reaction (PCR)-positive infection, biopsy-proven malignancy and Diabetes Mellitus.

19. Statistical Methods

The details below are examples only. Complete this section as described in the protocol.

All analysis approaches follow the OUTSMART Statistical Analysis Plan (SAP) v2.4 090221 and use the intention to treat population unless otherwise stated here. All analyses were reported as treatment estimates with 95% CIs, with results considered "statistically significant" at 5% significance. No formal adjustments were made for multiple testing.

Analyses estimate the following treatment effect contrasts for the primary and secondary outcomes:

1a. Unblinded Biomarker Led Care versus Blinded Standard Care in HLA Ab Positive DSA participants (both at randomisation and re-screening)

1b. Unblinded Biomarker Led Care arm versus Blinded Standard Care in HLA Ab Positive Non-DSA participants (both at randomisation and re-screening)

2. Unblinded Care versus Blinded Care in all randomised participants

For the primary outcome, contrasts 1a and 1b were tested for superiority (as per the SAP) and contrast 2 was tested for non-inferiority, with non-inferiority concluded if the upper bound of the 95% confidence interval for the hazard ratio was less than 1.4. For all secondary outcomes, all contrasts were tested for superiority.

The primary outcome of time to graft failure was modelled using Cox proportional hazards regression models, adjusted for the randomisation stratification factors of previous immunosuppression regimen and research site. Within the 1a and 1b contrasts, time zero was i) time of randomisation for participants who were HLA Ab positive at randomisation, and ii) time of re-screening for participants who were HLA Ab positive at rescreening. Participants follow up time was taken up until the pre-COVID-19 collection period. The proportional hazards assumption was checked by examining Kaplan Meier plots and by testing for an interaction between treatment and time (more precisely, testing for a non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals on functions of time which is equivalent to testing the interaction).

The analysis of the secondary outcome of time to death (all-cause mortality) was modelled in the same way as the primary outcome. An additional analysis restricting the follow up time to the first 32 months was carried out for time to death (as the original protocol implied that all secondary outcomes will be carried out on the 32 months intensive follow up period only).

The secondary outcomes of biopsy proven rejection, infection, malignancy, and diabetes de novo were all analysed using logistic regression, with the outcome as to whether the participant experienced the event (at least once) over the intensive 32 month follow up period (from randomisation or from re-screening as appropriate). Site was not included as a covariate in these models, as small numbers recruited in some sites would lead to perfect prediction and observations being dropped. Baseline immunosuppression was included as a covariate as per the primary outcome model. All participants were included if they had at least one observation post-randomisation (or post-rescreening).

The outcome of proteinuria at month 32 was analysed using a logistic (longitudinal) mixed model, with all observations included between randomisation (or re-screening as appropriate) and month 32 at 4 monthly intervals, although most participants only had data at 8 monthly intervals as frequency of follow up was changed to 8 monthly in Protocol V10 11/08/2015). Trial arm, timepoint, an interaction between timepoint and trial arm and stratification factors were included as covariates. A random intercept was included for participant. Treatment effects at month 32 were estimated using post-

estimation commands. All participants were included if they had at least one observation post-randomisation (or post-rescreening).

The outcome of eGFR was analysed using a linear (longitudinal) mixed model, with timepoints as per the proteinuria model. Trial arm, timepoint, an interaction between timepoint and trial arm, baseline eGFR and the stratification factors were included as covariates. A random intercept was included for participant. Treatment effects at month 32 were estimated using post-estimation commands. All participants were included if they had at least one observation post-randomisation or post-rescreening (and so estimates are unbiased under a missing at random assumption as the model uses maximum likelihood).

Several sensitivity analyses were carried out for the primary outcome. These used the same covariates/modelling strategy as the primary analysis unless stated:

1. Excluding site as a covariate: There were a large number of sites, and this was a stratification factor adjusted for the model. However, there were low numbers of participants recruited for some sites such that some estimates for the site covariate was not estimated in the model. An analysis excluding site was carried out to ensure this was not causing instability in treatment effect estimates.

2. A competing risks analysis using competing risk regression, according to the method of Fine and Gray (1999), was carried out to examine sensitivity of the results to the competing risk of death. The sub-hazard ratio for graft failure was estimated.

3. For COVID19 data: An analysis was carried out using additional follow up data up until November 30th, 2020, which we called the post-COVID-19 timepoint as these participants' outcomes may have been affected by the COVID-19 pandemic. The analysis was otherwise exactly the same.

4. Using same model within the HLA Non-DSA group but restricting it to those participants who were assessed as definite non-DSA (as opposed to Non-DSA in the absence of any conclusive evidence of DSA)

5. A sensitivity analysis/per protocol type analysis was also carried out restricting those in the HLA Ab+ DSA and HLA Ab+ non-DSA groups to those who received the full optimisation protocol (taking MMF, Tacrolimus and Prednisolone at the visit following the optimisation interview).

20. Summary – Conclusions

20.1 Demographic data

Summary data can be included here. It is mandatory to provide details on gender and age of the treated subjects at a minimum for EudraCT.

The following tables summarise the demographics/clinical characteristics at baseline of the entire sample. Treated subjects are those in the HLA Ab+ DSA BLC and HLA Ab+ Non-DSA BLC groups as per tables below. Participants in the sample were aged 18-75 as per inclusion/exclusion criteria and this range was the same across all groups. Below, there are characteristics for two different groupings. The grouping at randomisation is baseline characteristics by group at baseline. Post-rescreening grouping are the characteristics at baseline for those participants who didn't switch groups at re-screening, and a substituted baseline for those participants who did switch groups at re-screening (as became HLA positive), with the baseline measure substituted with the new "clock-reset" baseline (visit at which they were re-screened).

Table 4 - Baseline characteristics / Demographic data

Group	HLA Positive DSA				HLA Positive Non-DSA				HLA Negative				
	Blinded (SC) A1		Unblinded (BLC) B1		Blinded (SC) A2		Unblinded (BLC) B2		Blinded (SC) C		Unblinded (BLC) D		
Sample used	**Randomisation (N=64)**	**Post-Screening (N=92)**	**Randomisation (N=71)**	**Post-Screening (N=106)**	**Randomisation (N=275)**	**Post-Screening (N=391)**	**Randomisation (N=280)**	**Post-Screening (N=427)**	**Randomisation (N=670)**	**Post-Screening (N=526)**	**Randomisation (N=677)**	**Post-Screening (N=495)**	**To (Rando ion c (N=2**
Age (years) *Mean (SD)*	49.5 (12.0)	48.1 (13.7)	47.0 (14.6)	46.8 (14.0)	50.0 (11.9)	49.4 (12.7)	50.6 (12.6)	50.3 (12.6)	50.3 (13.30)	51.1 (12.7)	50.5 (13.2)	51.0 (13.3)	50.20 (
Gender - Male *(%)*	65.6	71.7	80.3	81.1	55.6	61.1	58.6	58.8	73.3	72.4	72.1	75.2	68
Ethnicity *(%)*													
Asian	9.4	9.9	14.1	12.3	12.7	12.3	13.2	13.6	11.3	11.4	12.9	12.7	12
Black	18.8	16.3	14.1	12.3	7.6	10.0	11.4	12.2	10.6	9.5	9.7	8.7	10
White	68.8	71.7	70.4	73.6	75.6	74.2	72.1	71.4	75.1	75.9	74.7	75.8	74
Mixed	1.1	1.1	0	0	1.5	1.5	1.4	0.9	0.6	0.4	0.1	0.2	0.
Other	1.6	1.1	1.4	1.9	2.5	2.0	1.8	1.9	2.4	2.9	2.5	2.6	2.
Site *(n,%)*													
Leeds	8 (2.7)	11 (3.8)	8 (2.7)	12 (4.1)	41 (14.1)	70 (24.1)	40 (13.7)	76 (26.1)	96 (33.0)	64 (22.0)	98 (33.7)	58 (19.9)	291 (
Royal London	6 (4.6)	8 (6.2)	5 (3.8)	8 (6.2)	11 (8.5)	17 (13.1)	12 (9.2)	18 (13.8)	48 (36.9)	40 (30.8)	48 (36.9)	39 (30.0)	130
GSTT	21 (4.0)	32 (6.0)	24 (4.5)	34 (6.4)	69 (13.0)	105 (19.8)	72 (13.6)	121 (22.9)	170 (32.1)	123 (23.3)	173 (32.7)	114 (21.6)	529 (
Manchester	8 (2.6)	12 (3.8)	8 (2.6)	9 (2.9)	44 (14.1)	50 (16.0)	47 (15.1)	54 (17.3)	103 (33.0)	93 (29.8)	102 (32.7)	94 (30.1)	312 (
Birmingham	3 (1.4)	5 (2.3)	2 (0.9)	12 (5.5)	31 (14.3)	47 (21.7)	27 (12.4)	42 (19.4)	77 (35.5)	59 (27.2)	77 (35.5)	52 (24.0)	217 (
King's	6 (4.2)	8 (5.6)	4 (2.8)	5 (3.5)	21 (14.7)	29 (20.3)	21 (14.7)	28 (19.6)	44 (30.8)	34 (23.8)	47 (32.9)	39 (27.3)	143
York	2 (3.8)	4 (7.5)	2 (3.8)	4 (7.5)	6 (11.3)	9 (17.0)	7 (13.2)	16 (30.2)	18 (34.0)	13 (24.5)	18 (34.0)	7 (13.2)	53 (
Coventry	0 (0.0)	0 (0.0)	1 (1.9)	2 (3.8)	6 (11.3)	8 (15.1)	7 (13.2)	12 (22.6)	18 (34.0)	16 (30.2)	21 (39.6)	15 (28.3)	53 (
Preston	1 (1.5)	2 (3.1)	4 (6.2)	5 (7.7)	11 (16.9)	13 (20.0)	8 (12.3)	12 (18.5)	21 (32.3)	18 (27.7)	20 (30.8)	15 (23.1)	65 (
Salford	1 (1.9)	1 (1.9)	1 (1.9)	1 (1.9)	6 (11.5)	8 (15.4)	8 (15.4)	8 (15.4)	19 (36.5)	17 (32.7)	17 (32.7)	17 (32.7)	52 (
Bradford	3 (6.2)	3 (6.2)	5 (10.4)	7 (14.6)	8 (16.7)	8 (16.7)	9 (18.8)	12 (25.0)	12 (25.0)	12 (25.0)	11 (22.9)	6 (12.5)	48 (
Royal Free	5 (4.0)	5 (4.0)	6 (4.8)	6 (4.8)	18 (14.4)	24 (19.2)	19 (15.2)	22 (17.6)	38 (30.4)	32 (25.6)	39 (31.2)	36 (28.8)	125
St Helier	0 (0.0)	1 (5.3)	1 (5.3)	1 (5.3)	3 (15.8)	3 (15.8)	3 (15.8)	6 (31.6)	6 (31.6)	5 (26.3)	6 (31.6)	3 (15.8)	19 (
Cause of renal failure *n (%)*													
Diabetes	4 (6.9)	5 (6)	2 (3.4)	7 (8)	7 (2.9)	17 (5.1)	13 (5.4)	22 (5.9)	38 (6.7)	27 (6)	40 (6.8)	26 (6.1)	104
Glomerulonephritis	22 (37.9)	28 (33.7)	19(32.8)	30 (34.1)	93 (38.8)	128 (38.3)	94 (39.3)	147 (39.7)	216 (38.1)	175 (39.1)	224 (38.4)	160 (37.8)	668 (

Group	HLA Positive DSA				HLA Positive Non-DSA				HLA Negative				
	Blinded (SC) A1		Unblinded (BLC) B1		Blinded (SC) A2		Unblinded (BLC) B2		Blinded (SC) C		Unblinded (BLC) D		
Sample used	**Randomisation (N=64)**	**Post-Screening (N=92)**	**Randomisation (N=71)**	**Post-Screening (N=106)**	**Randomisation (N=275)**	**Post-Screening (N=391)**	**Randomisation (N=280)**	**Post-Screening (N=427)**	**Randomisation (N=670)**	**Post-Screening (N=526)**	**Randomisation (N=677)**	**Post-Screening (N=495)**	**To (Rando ion c (N=2**
Polycystic kidney disease	7 (12.1)	10 (12)	9 (15.5)	12 (13.6)	32 (13.3)	45 (13.5)	34 (14.2)	54 (14.6)	105 (18.5)	89 (19.9)	100 (17.1)	77 (18.2)	287 (
Hypertension	6 (10.3)	7 (8.4)	6 (10.3)	7 (8)	20 (8.3)	28 (8.4)	22 (9.2)	34 (9.2)	43 (7.6)	34 (7.6)	47 (8)	34 (8)	144
Congenital	7 (12.1)	13 (15.7)	7 (12.1)	10 (11.4)	31 (12.9)	41 (12.3)	22 (9.2)	34 (9.2)	66 (11.6)	50 (11.2)	47 (8)	32 (7.6)	180 (
Obstructive	8 (13.8)	12 (14.5)	10(17.2)	16 (18.2)	38 (15.8)	50 (15)	34 (14.2)	48 (13)	54 (9.5)	38 (8.5)	80 (13.7)	60 (14.2)	224 (
Other	4 (6.9)	8 (9.6)	5 (8.5)	6 (6.7)	19 (7.8)	25 (7.5)	20 (8.3)	31 (8.4)	45 (8.1)	35 (7.7)	46 (7.9)	34 (7.9)	139 (
Previous transplants *n(%)]*													
0	48 (76)	71 (78)	52(73.2)	85 (80.2)	193(70.7)	301 (77.4)	198 (70.7)	337 (79.1)	613 (91.5)	482 (92)	633 (94.1)	461 (93.9)	1737 (8
1	12 (19)	17 (18.7)	18(25.4)	20 (18.9)	71 (26)	79 (20.3)	65 (23.3)	73 (17.1)	55 (8.2)	42 (8)	35 (5.2)	25 (5.1)	256 (1
2	3 (4.8)	3 (3.3)	1 (1.4)	1 (0.9)	8 (2.9)	8 (2.1)	13 (4.7)	13 (3.1)	0 (0)	0 (0)	5 (0.7)	5 (1)	30 (1
3	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.4)	1 (0.3)	3 (1.1)	3 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	4 (0.
Time (years) since Tx *Median (IQR)*	6.6 (3.0-12.0)	5.9 (3.0-11.9)	9.7 (3.9-14.3)	6.7 (3.0-12.4)	5.7 (2.2-10.9)	5.4 (2.2-9.8)	4.9 (2.3-11.2)	5.1 (2.4-10.8)	5.4 (2.4-9.2)	5.4 (2.4-9.6)	5.1 (2.4-9.7)	5.1 (2.4-9.8)	5.4 (2 10.
Taking **CsA** n (%)	17 (27)	26 (28)	18 (25)	22 (21)	49 (18)	69 (18)	49 (18)	74 (17)	121 (18)	90 (17)	120 (18)	89 (18)	374
Mean Dose (SD)	170.3 (49.8)	187.3 (62.8)	199.4 (68.5)	199.6 (63.6)	168.6 (65.0)	174.4 (62.5)	168.7 (60.4)	160.6 (58.9)	180.7(67.9)	176.3 (67.8)	168.7 (63.0)	174.7 (62.9)	174 (64
Mean trough level (SD)	72.3 (34.8)	89.3 (56.2)	80.9 (55.3)	80.7 (51.5)	102.8 (84.8)	101.2 (79.8)	88.6 (56.1)	87.3 (52.0)	100 (71.4)	91.9 (52.3)	109.6 (88.5)	116.4 (97.2)	99 (76
Taking **Tac** n(%)	39 (61)	56 (61)	41 (58)	67 (64)	205 (75)	296 (76)	205 (73)	313 (73)	499 (74)	392 (75)	501 (74)	366 (74)	1490
Mean dose (SD)	6.14 (6.72)	6.18 (5.97)	4.01 (2.24)	4.62 (3.33)	5.08 (3.51)	5.14 (3.66)	5.60 (4.60)	5.41 (4.39)	5.50 (4.12)	5.44 (4.13)	4.89 (3.65)	4.70 (3.15)	5.23 (
Mean trough level (SD)	6.49 (2.64)	6.56 (2.86)	5.65 (2.06)	5.83 (2.18)	6.95 (2.93)	6.88 (2.74)	6.86 (2.29)	6.68 (2.21)	6.91 (2.31)	6.93 (2.26)	6.71 (2.47)	6.72 (2.52)	6.79 (
Taking **MMF** n(%)	40 (63)	59 (64)	41 (58)	62 (59)	177 (64)	254 (65)	176 (63)	271 (63)	460 (69)	361 (69)	471 (70)	351 (71)	1365
Mean dose (SD)	1156 (476)	1165 (482)	1098 (422)	1145 (399)	1131 (450)	1134 (457)	1117 (483)	1112 (472)	1155 (490)	1147 (495)	1136(466)	1136 (473)	1138
Taking **Aza** n(%)	15 (23)	19 (21)	19 (27)	26 (25)	52 (19)	66 (17)	39 (14)	61 (14)	90 (13)	71 (13)	94 (14)	69 (14)	309
Mean dose (SD)	88.3 (45.2)	90.8 (43.5)	69.7 (33.9)	76.9 (32.3)	76.7 (43.3)	78.2 (40.8)	86.5 (39.3)	88.5 (39.4)	85.3 (34.7)	85.2 (33.4)	85.1 (35.1)	83.6 (35.9)	83.1 (

Group	HLA Positive DSA				HLA Positive Non-DSA				HLA Negative				
	Blinded (SC) A1		Unblinded (BLC) B1		Blinded (SC) A2		Unblinded (BLC) B2		Blinded (SC) C		Unblinded (BLC) D		
Sample used	**Randomisation (N=64)**	**Post-Screening (N=92)**	**Randomisation (N=71)**	**Post-Screening (N=106)**	**Randomisation (N=275)**	**Post-Screening (N=391)**	**Randomisation (N=280)**	**Post-Screening (N=427)**	**Randomisation (N=670)**	**Post-Screening (N=526)**	**Randomisation (N=677)**	**Post-Screening (N=495)**	**To (Rando ion c (N=2**
Taking Sirolimus n(%)	2 (3.1)	2 (2.2)	5 (7.0)	6 (5.7)	10 (3.6)	10 (2.6)	4 (1.4)	6 (1.4)	17 (2.5)	16 (3.0)	25 (3.7)	18 (3.6)	63 (
Mean dose (SD)	2.50 (0.71)	2.50 (0.71)	1.60 (0.55)	1.50 (0.55)	2.00 (0.82)	2.00 (0.82)	2.00 (0.82)	2.00 (0.89)	1.65 (0.70)	1.62 (0.72)	2.00 (0.91)	2.06 (0.80)	1.89 (
Taking Everolimus n(%)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	3 (0.4)	3 (0.6)	0 (-)	0 (-)	3 (0
Mean dose (SD)	-		-	-	-	-	-	-	2.33 (0.58)	2.33 (0.58)	-	-	2.33 (
Taking Prednisolone n(%)	37 (58)	53 (58)	38 (54)	62 (59)	153 (56)	210 (54)	154 (55)	227 (53)	369 (55)	295 (56)	372 (55)	274 (55)	1123
Mean dose (SD)	4.97 (1.72)	5.16 (1.81)	4.97 (2.13)	5.10 (1.87)	4.99 (1.45)	5.01 (1.39)	4.99 (1.62)	5.13 (1.58)	5.08 (1.67)	5.11 (1.75)	5.20 (1.62)	5.11 (1.43)	
Taking Tac /MMF/Pred N (%)	13 (20)	19 (21)	13 (18)	24 (23)	82 (30)	114 (29)	70 (25)	106 (25)	192 (29)	152 (29)	189 (28)	139 (28)	559
Creatinine[12] *Mean (SD)*	128.97 (40.32)	129.09 (39.30)	124.96 (37.29)	126.06 (38.25)	123.23 (35.42)	124.08 (35.23)	122.61 (35.81)	121.17 (35.25)	126.17 (38.78)	126.02 (39.71)	126.73 (36.76)	129.07 (36.96)	125 (37.
eGFR[13] *Mean (SD)*	52.31 (15.36)	52.93 (15.23)	56.27 (17.70)	56.16 (18.01)	52.12 (16.54)	52.80 (16.39)	52.89 (16.32)	54.12 (17.30)	53.77 (15.90)	53.59 (15.95)	53.76 (17.26)	52.82 (16.57)	53. (16.
PCR[14] *Median (IQR)*	26.50 (15.50-48.25)	26.50 (13.75-49.75)	16.50 (10.75-39.25)	23.50 (13.00-49.50)	18.00 (8.00-37.25)	18.00 (8.00-38.00)	20.00 (9.00-42.50)	19.00 (9.00-37.25)	17.00 (9.00-41.25)	17.00 (9.00-39.00)	21.00 (10.00-41.00)	21.00 (10.00-43.00)	19.00 41.(
ACR[14] *Median (IQR)**	1.90 (1.40-1.95)	2.00 (1.90-45.60)	5.30 (2.75-7.85)	2.30 (0.80-8.00)	2.80 (1.30-6.30)	2.80 (1.20-7.70)	7.05 (3.13-15.10)	6.40 (2.82-20.10)	3.20 (1.20-12.20)	3.20 (1.35-9.22)	3.30 (0.95-10.20)	2.55 (0.90-8.75)	3.30 (9.6

[12] μmol/L
[13] mls/min/1.73 m^2
[14] mg/mmol
*ACR only recorded for some participants where site used ACR instead of PCR.

Table 5 - Overall age categorised

Age category	Blinded Care	Unblinded Care	Total
18-64	878 (87.0%)	889 (86.5%)	1767 (86.7%)
65-84	131 (13.0%)	139 (13.5%)	270 (13.3%)

87% of participants were between the ages of 18-64, with 13% 65 or over.

20.2 Primary outcome

All treatment estimates are given as the HLA Ab Unblinded (Biomarker-led care) arm compared to the HLA Ab Blinded (Standard care) arm. For the primary outcome analysis (and subsequent sensitivity analyses), 2 randomised participants (in the HLA negative group) were not included in the analysis for the All participants group as they had no follow up data after randomisation. 1 randomised participant was not included in the DSA group as they were found to have graft failure prior to being re-screened and becoming HLA +ve DSA and so were not at risk for the purpose of this analysis.

Primary outcome (Time to graft failure) results

Table 6 - Primary outcome results

Group/Comparison	Hazard Ratio	P-value	Lower 95% CI	Upper 95% CI
DSA (N=197)	1.54	0.27	0.72	3.30
Non-DSA (N=818)	0.97	0.91	0.54	1.74
All participants (N=2035)	1.02	0.93	0.72	1.44

There was no evidence for superiority of the unblinded/ biomarker led care strategy compared to the blinded/standard care strategy in either the HLA AB DSA or HLA AB non-DSA groups for graft failure with 95% confidence intervals. There was insufficient evidence for the non-inferiority of the Unblinded care strategy overall as the upper 95% confidence limit for the hazard ratio exceeded the pre-specified threshold of 1.4.

Figure 2 - Time to graft failure Kaplan Meier plot for DSA group

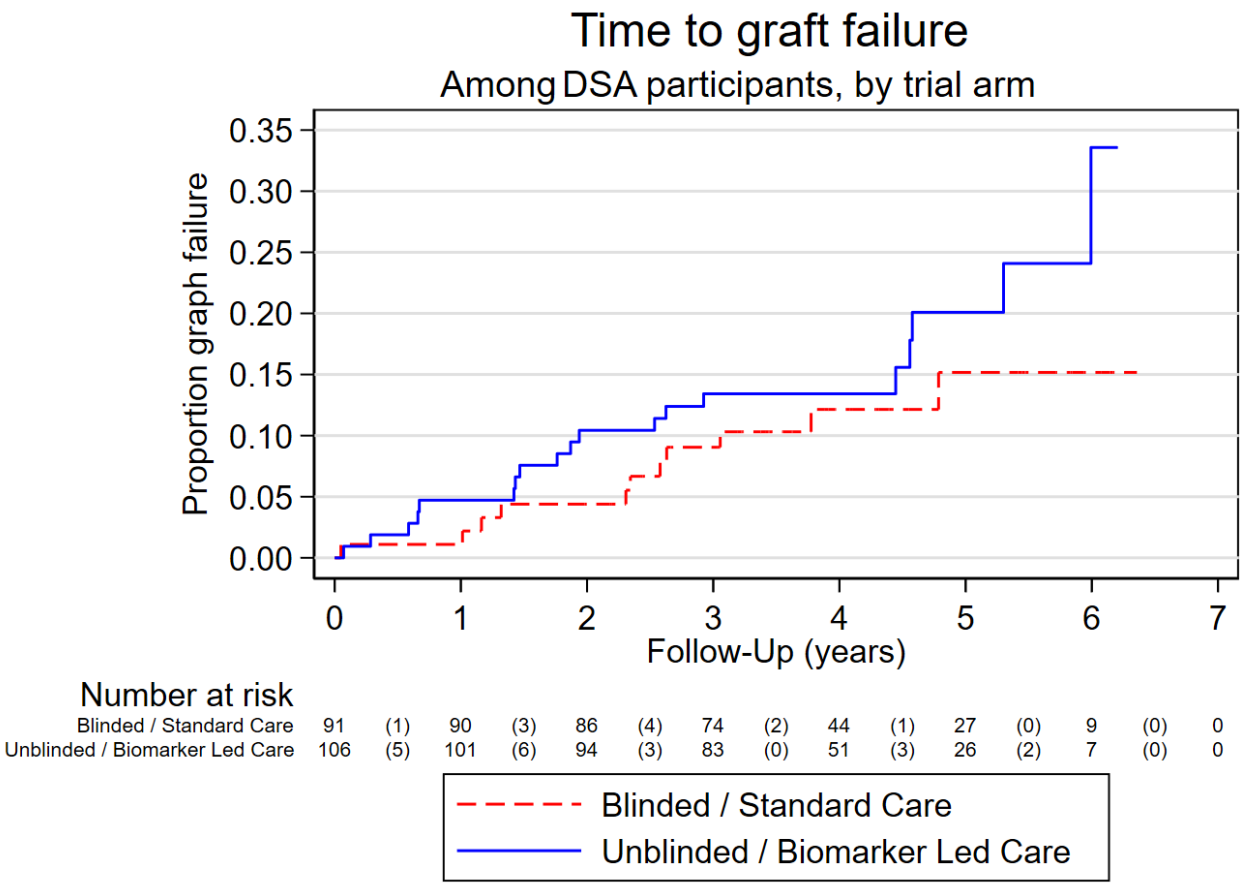


Figure 3 - Time to graft failure Kaplan Meier plot for non-DSA group

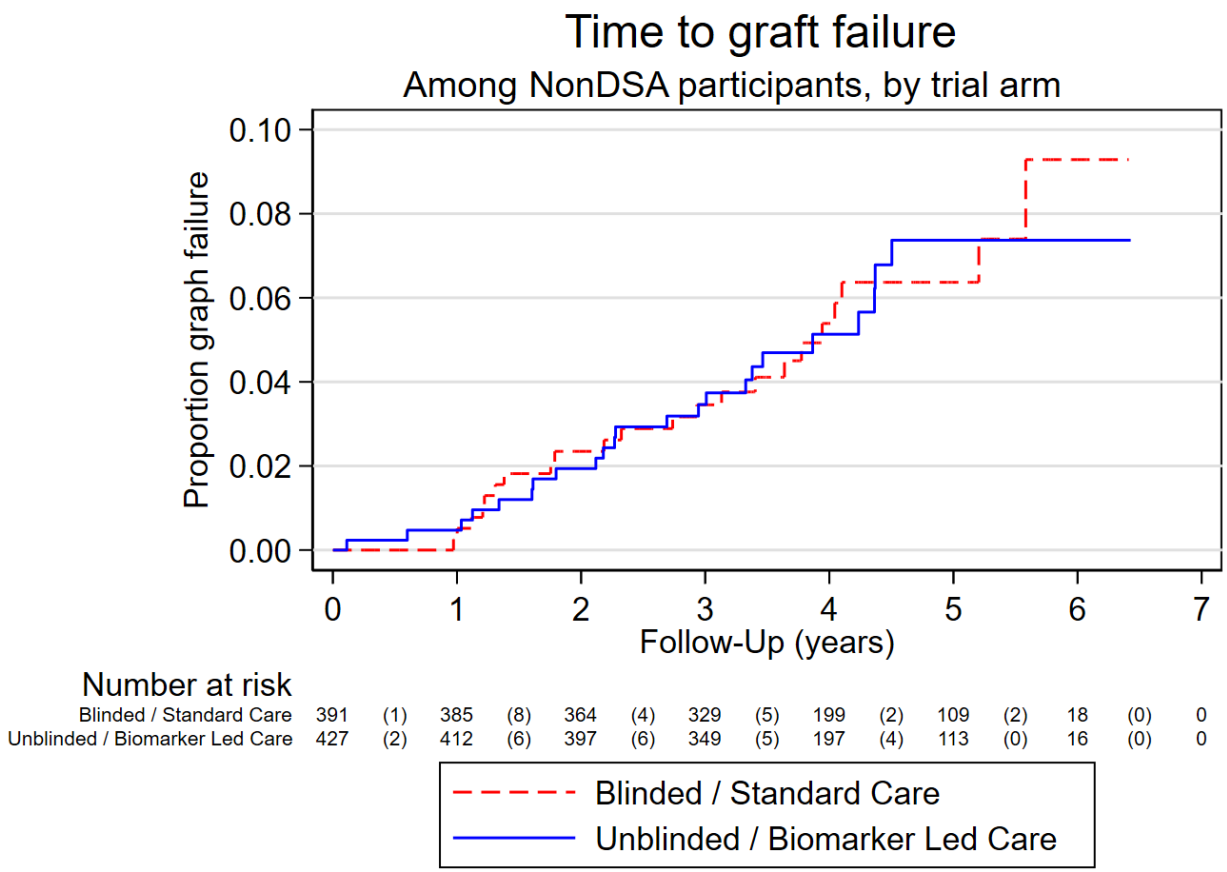


Figure 4 - Time to Graft failure Kaplan Meier for all participants

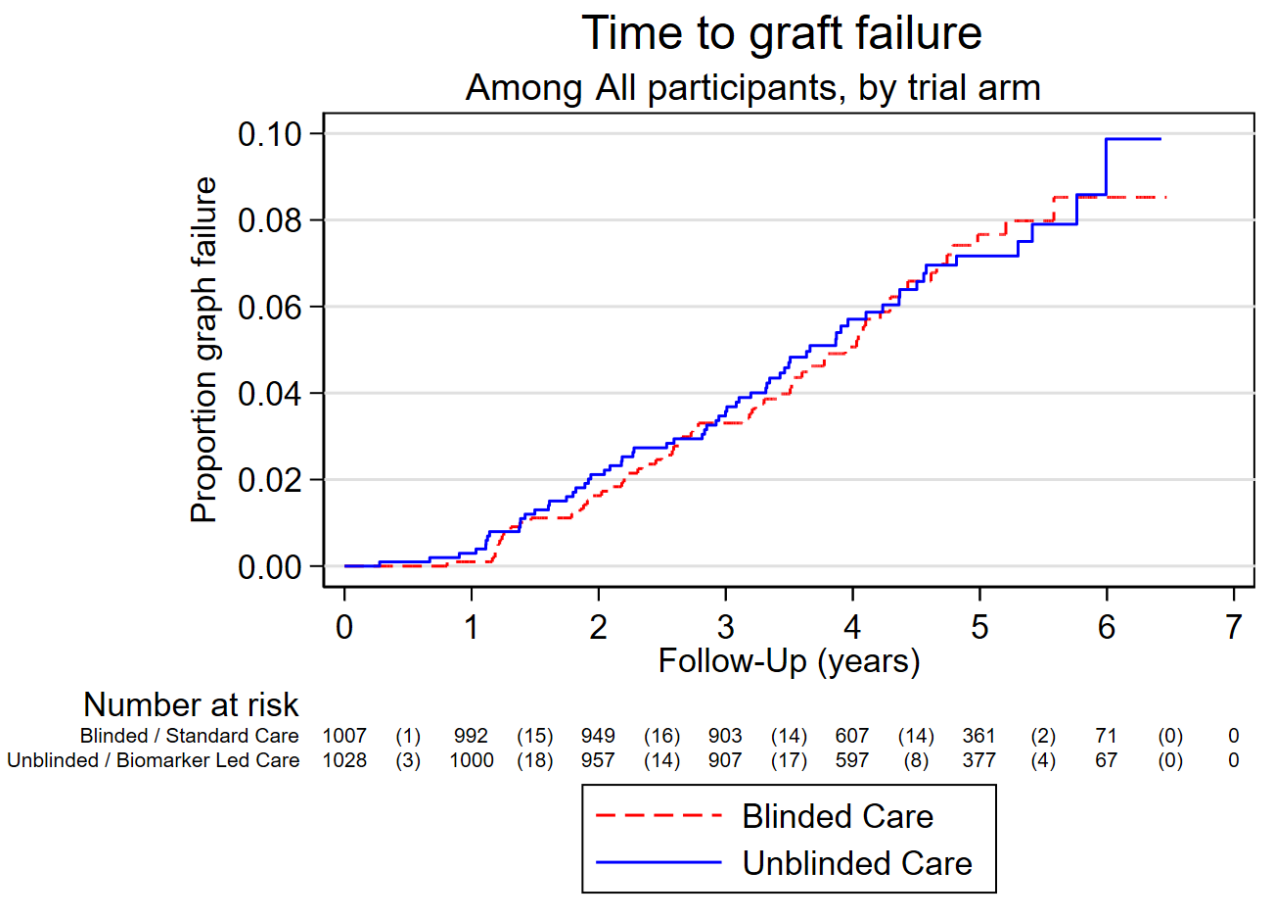


Table 7 – Summary of Graft Failures by year of follow up by HLA group and Trial Arm

This table uses the actuarial life table approach for estimating cumulative proportion of graft failures (GF) over time (as summarising using fixed intervals) and estimates may not match Kaplan Meier plots exactly (which use the product limit approach for continuous time).

	DSA BLC (B1)			DSA SC (A1)				Non-DSA BLC (B2)			Non DSA SC (A2)			Neg Blinded (C)			Neg Unblinded (D)	
Follow up (Years)	**N at risk**	**GF**	**Estimated Cumulative proportion**	**N at risk**	**GF**	**Estimated Cumulative proportion**	**N at risk**	**GF**	**Estimated Cumulative proportion**	**N at risk**	**GF**	**Estimated Cumulative proportion**	**N at risk**	**GF**	**Estimated Cumulative proportion**	**N at risk**	**GF**	**Estimated Cumulative proportion**
0-1	106	5	0.047	91	1	0.011	427	2	0.005	391	1	0.003	524	1	0.002	495	2	0.004
1-2	101	6	0.104	90	3	0.044	412	6	0.019	385	8	0.024	514	6	0.014	476	6	0.017
2-3	94	3	0.134	86	4	0.091	397	6	0.035	364	4	0.035	490	9	0.032	454	3	0.024
3-4	83	0	0.134	74	2	0.121	350	5	0.053	329	5	0.053	466	5	0.045	434	10	0.051
4-5	51	3	0.199	44	1	0.146	199	4	0.076	200	2	0.065	297	7	0.073	277	0	0.051
5-6	26	2	0.290	27	0	0.146	113	0	0.076	109	2	0.094	172	0	0.073	172	1	0.060
6-7	7	0	0.290	9	0	0.146	17	0	0.076	19	0	0.094	28	0	0.073	30	0	0.060

Sensitivity analyses for primary outcome

Sensitivity excluding site as covariate

Table 8 - Sensitivity without site for primary outcome

Group/Comparison	Hazard Ratio	Lower 95% CI	Upper 95% CI	P-value
DSA (N=197)	1.51	0.72	3.19	0.28
Non-DSA (N=818)	0.98	0.54	1.75	0.93
All participants (N=2035)	1.02	0.72	1.45	0.91

A sensitivity analysis excluding site as a covariate was carried out to check that the low numbers in some sites was not impacting the estimates. This showed that estimates are very similar in both analyses and so there was no suggestion that this was an issue for the primary analysis.

Competing risk sensitivity

Table 9 - competing risk sensitivity analysis results for primary outcome

Group/Comparison	Sub-Hazard Ratio	Lower 95% CI	Upper 95% CI	P-value
DSA (N=197)	1.53	0.70	3.35	0.29
Non-DSA (N=818)	0.96	0.53	1.74	0.90
All participants (N=2035)	1.01	0.71	1.43	0.96

The effect estimates for time to graft failure did not change appreciably when the competing risk of death was allowed for. This suggested that intercurrent deaths did not bias the primary analysis estimates.

Sensitivity – Post-COVID-19

Table 10 - Post-COVID-19 sensitivity analysis results for primary outcome

Group/Comparison	Hazard Ratio	Lower 95% CI	Upper 95% CI	P-value
DSA (N=197)	1.29	0.64	2.60	0.48
Non-DSA (N=818)	1.05	0.61	1.82	0.86
All participants (N=2035)	1.03	0.74	1.42	0.88

The analyses of the primary outcome were also repeated including additional graft failure events that occurred between March 18th, 2020, and November 2020, (i.e., which were likely to be affected by COVID-19). These analyses provided similar estimates. The hazard ratio in the DSA group was slightly lower than for the primary result (for Unblinded compared to blinded) but the 95% confidence interval remained wide and included the null value, one. The other two hazard ratios remained close to the null.

Sensitivity – using time zero as randomisation for DSA and Non-DSA re-screened participants

Table 11 - Time zero for all sensitivity analysis results for primary outcome

Group/Comparison	Hazard Ratio	Lower 95% CI	Upper 95% CI	P-value
DSA (N=197)	1.35	0.64	2.86	0.43
Non-DSA (N=818)	0.96	0.53	1.72	0.88

A sensitivity analysis using randomisation as time zero for all participants (instead of time of re-screening) within DSA and non-DSA groups (regardless of when they become HLA positive). Again, this gave similar estimates as in the main primary outcome analysis.

Sensitivity – only including optimised participants in BLC care arm

Table 12 - Optimised Unblinded participants only sensitivity analysis results for primary outcome

Group/Comparison	Hazard Ratio	Lower 95% CI	Upper 95% CI	P-value
DSA (N=145)	1.17	0.44	3.14	0.75
Non-DSA (N=569)	0.96	0.44	2.10	0.91
All participants (N=1238)	1.21	0.71	2.09	0.48

A sensitivity analysis (per-protocol type analysis) restricting the Unblinded (BLC) arm to participants who were optimised in the DSA/Non-DSA groups showed no appreciable difference to the primary analyses.

Sensitivity – only definite non-DSA participants included in Non-DSA group, unknown whether DSA included in DSA group

Table 13 - Optimised Unblinded participants only sensitivity analysis results for primary outcome

Group/Comparison	Hazard Ratio	Lower 95% CI	Upper 95% CI	P-value
DSA (N=283)	1.47	0.76	2.85	0.25
Non-DSA (N=729)	0.90	0.46	1.73	0.74

A sensitivity analysis where those participants who were screened as "Unknown whether DSA" were included in the DSA group rather than the non-DSA group again showed no appreciable differences from the primary analysis.

Secondary clinical outcomes

Death (All-Cause Mortality)

Table 14 - Results for secondary outcome of death - using all follow up time

Group/Comparison	Hazard Ratio	Lower 95% CI	Upper 95% CI	P-value
DSA – using all follow up time (N=197)	2.33	0.57	9.57	0.24
Non-DSA – using all follow up time (N=818)	1.24	0.76	2.02	0.40
All participants – using all follow up time (N=2035)	1.14	0.85	1.54	0.38

Table 15 - Results for secondary outcome of death - using up to M32 intensive follow up only

Group/Comparison	Hazard Ratio	Lower 95% CI	Upper 95% CI	P-value
DSA – up to month 32 follow up only (N=197)	Not enough events to estimate	Fisher's exact test		Deaths (1 blinded, 0 Unblinded) p=0.47
Non-DSA – up to month 32 follow up only (N=818)	1.21	0.52	2.76	0.66
All participants – up to month 32 follow up only (N=2035)	1.31	0.81	2.10	0.27

The hazard ratio in the DSA group was just over 2 but the 95% CI was extremely wide reflecting the imprecision of the estimate due to the low number of deaths, and findings are consistent with there being no difference.

The results were similar when the analyses were restricted to the 32 months intensive follow up period. There were insufficient events in the DSA group (N=1) to carry out a Cox regression and so a Fisher's exact test was used which was not statistically significant difference (P=0.47).

Biopsy proven rejection, PCR confirmed infections, malignancy and Diabetes Mellitus de novo

Table 16 - Results for biopsy proven rejection, confirmed infections, malignancy, and diabetes secondary outcomes

Outcome / Group	Odds Ratio	Lower 95% CI	Upper 95% CI	P-value
Biopsy Proven rejection – DSA (N=157)	0.39	0.11	1.37	0.14
Biopsy Proven rejection – Non-DSA (N=710)	0.58	0.19	1.80	0.35
Biopsy Proven rejection – All (N=2035)	0.54	0.28	1.01	0.06
PCR confirmed infection – DSA (N=197)	1.75	0.89	3.44	0.10
PCR confirmed infection – Non-DSA (N=809)	1.09	0.79	1.50	0.62
PCR confirmed infection – All (N=2010)	1.00	0.84	1.19	0.96
Malignancy – DSA (N=198)	1.08	0.36	3.28	0.89
Malignancy – Non-DSA (N=810)	0.93	0.57	1.52	0.77
Malignancy – All (N=2015)	0.92	0.65	1.31	0.65
Diabetes Mellitus de novo – DSA (N=198)	0.99	0.19	5.21	0.99
Diabetes Mellitus de novo – Non-DSA (N=818)	0.56	0.25	1.26	0.16
Diabetes Mellitus de novo – All (N=2015)	0.75	0.41	1.37	0.34

These outcomes are all binary variables as to whether the participant experienced the event of interest between randomisation and 32 months intensive follow up (or between re-screening and 32 months intensive follow up for rescreened participants). For the overall comparison, the odds of biopsy proven rejection were lower in the Unblinded BLC group than in the blinded SC group (0.54, 95% CI 0.28 - 1.01) but this did not quite reach the p<0.05 threshold (p=0.06). There was no evidence of a difference in odds of experiencing the event for any other outcomes/groups.

eGFR

Table 17 - Results for secondary outcome of eGFR

Outcome	Mean Difference	Lower 95% CI	Upper 95% CI	P-value
DSA – eGFR at Month 32	0.91	-2.83	4.65	0.63
Non-DSA – eGFR at Month 32	0.24	-1.50	1.98	0.78
All participants - eGFR at Month 32	-0.46	-1.98	1.05	0.55

There was no evidence for a difference in mean eGFR between groups with very small mean differences for all.

Proteinuria (as defined)

Table 18 - Results for secondary outcome of Proteinuria

Outcome	Odds Ratio	Lower 95% CI	Upper 95% CI	P-value
DSA – Proteinuria at Month 32	0.28	0.05	1.59	0.15
Non-DSA – Proteinuria at Month 32	1.47	0.61	3.53	0.39
All participants - Proteinuria at Month 32	0.80	0.47	1.37	0.42

There was no evidence of a difference in the odds of experiencing Proteinuria at Month 32 between groups.

Secondary health beliefs outcomes

1. **A comparison of how adherence to drug therapy and perceptions of risk in the BLC DSA+ and the BLC non-DSA+ groups changed from baseline to post-treatment.**

The impact of biomarker led care on adherence was assessed using descriptive statistics showing changes in the MARS between baseline (T1) and 12 months follow up (T2). Scores on the MARS are very strongly skewed towards high adherence (range 1-5). Therefore, no meaningful changes over time were detected.

Table 19 - *The impact of biomarker screening and treatment on patients' adherence to drug therapy*

	BLC DSA+			BLC Non-DSA			SC DSA+			SC Non-DSA		
	n_1	Mean (SD)	Median (IQR)	n_1	Mean (SD)	Median (IQR)	n_2	Mean (SD)	Median (IQR)	n_2	Mean (SD)	Median (IQR)
MARS Tacrolimus												
T1	47	4.87 (.18)	4.83 (.17)	234	4.88 (.15)	5.00 (.17)	39	4.76 (.64)	4.83 (.17)	222	4.88 (.22)	5.00 (.17)
T2	28	4.89 (.16)	5.00 (.17)	125	4.86 (.21)	4.83 (.17)	16	4.88 (.14)	4.83 (.17)	100	4.89 (.20)	5.00 (.17)
T3	46	4.88 (.19)	5.00 (.17)	184	4.86 (.22)	4.83 (.17)	26	4.86 (.17)	4.83 (.17)	157	4.89 (.13)	4.83 (.17)
T4	10	4.92 (.16)	5.00 (.17)	62	4.88 (.13)	4.83 (.17)	6	4.92 (.09)	4.92 (.17)	50	4.87 (.18)	4.92 (.17)
MARS Mycophenolate												
T1	40	4.89 (.32)	5.00 (.17)	212	4.89 (.19)	5.00 (.17)	39	4.76 (.65)	4.83 (.17)	190	4.88 (.23)	5.00 (.17)
T2	26	4.94 (.11)	5.00 (.17)	114	4.86 (.24)	5.00 (.17)	25	4.79 (.32)	4.83 (.17)	94	4.86 (.28)	5.00 (.17)
T3	44	4.85 (.26)	5.00 (.17)	167	4.89 (.16)	5.00 (.17)	30	4.87 (.13)	4.83 (.17)	143	4.87 (.16)	4.83 (.17)
T4	9	4.92 (.09)	5.00 (.17)	59	4.89 (.12)	4.83 (.17)	9	4.89 (.08)	4.83 (.17)	40	4.87 (.20)	4.92 (.17)
MARS Prednisolone												
T1	32	4.86 (.36)	5.00 (.17)	178	4.90 (.16)	5.00 (.17)	28	4.80 (.28)	4.83 (.17)	151	4.91 (.14)	5.00 (.17)
T2	26	4.83 (.40)	5.00 (.17)	97	4.87 (.27)	5.00 (.17)	20	4.72 (.34)	4.83 (.46)	68	4.93 (.14)	5.00 (.17)
T3	44	4.86 (.26)	5.00 (.17)	144	4.90 (.20)	5.00 (.17)	25	4.83 (.18)	4.83 (.25)	113	4.90 (.13)	5.00 (.17)
T4	12	4.85 (.38)	5.00 (.17)	48	4.91 (.15)	5.00 (.17)	7	4.83 (.10)	4.83 (.00)	25	4.89 (.12)	4.83 (.17)

T1: Baseline, T2: 12 months, T3: 24 months, T4: 24-month clock reset data. MARS: Medication Adherence Rating Scale.

The impact of biomarker led care on risk perceptions were assessed using descriptive statistics showing changes in the B-IPQ constructs. Few consistent differences were seen. For the item '*How much do you think HLA antibody testing can help reduce your risk of kidney transplant failure*?', improvements were seen in the BLC (DSA+ and Non-DSA) groups between baseline (T1) and 12 months (T2) / 24 months (T3). However, an improvement was also seen in the DSA+ SC group.

Concern about risk of transplant failure was reduced in the BLC groups (DSA+ and Non-DSA) from baseline (T1) to 12 months (T2). This concern increased in the SC DSA+ group and stayed relatively stable in the SC Non-DSA group.

Table 20 - The impact of biomarker screening and treatment on patients' illness perceptions

	BLC DSA+			BLC Non-DSA			SC DSA+			SC Non-DSA		
	n_1	Mean (SD)	Median (IQR)	n_2	Mean (SD)	Median (IQR)	n_1	Mean (SD)	Median (IQR)	n_2	Mean (SD)	Median (IQR)
Consequences												
T1	73	6.16 (3.61)	7.00 (7)	338	6.55 (3.59)	8.00 (7)	68	6.00 (3.89	7.00 (8)	305	6.55 (3.48)	8.00 (7)
T2	35	6.00 (3.38)	7.00 (7)	149	6.68 (3.40)	8.00 (7)	35	6.49 (3.24)	8.00 (6)	127	6.87 (3.27)	8.00 (6)
T3	62	5.48 (3.47)	5.00 (7)	224	6.35 (3.42)	7.50 (7)	42	5.93 (3.43)	6.50 (6)	217	6.35 (3.48)	8.00 (7)

T4	14	7.00 (3.53)	9.00 (7)	78	6.33 (3.41)	7.50 (7)		13	6.85 (3.58)	8.00 (7)	60	6.23 (3.59)	7.00 (7)
Control – Personal													
T1	73	6.30 (2.34)	7.00 (3)	333	5.86 (2.71)	6.00 (3)		68	6.07 (2.81)	7.00 (3)	303	5.86 (2.59)	6.00 (3)
T2	33	6.55 (2.11)	7.00 (3)	149	5.85 (2.56)	6.00 (4)		33	6.36 (2.07)	7.00 (3)	124	5.70 (2.48)	6.00 (4)
T3	62	6.06 (2.78)	6.50 (4)	223	6.00 (2.49)	6.00 (3)		42	6.19 (2.33)	6.50 (3)	216	5.99 (2.36)	6.00 (3)
T4	14	6.79 (2.12)	6.00 (4)	78	6.05 (2.43)	7.00 (3)		13	6.46 (3.01)	7.00 (5)	61	5.98 (2.12)	7.00 (4)
Control – Treatment													
T1	73	8.51 (1.57)	9.00 (2)	336	8.14 (2.05)	8.00 (3)		68	8.47 (1.64)	9.00 (2)	304	8.22 (1.86)	8.00 (2)
T2	32	8.16 (1.42)	8.00 (2)	149	7.99 (1.79)	8.00 (2)		34	8.24 (1.54)	8.00 (3)	128	8.34 (1.71)	9.00 (2)
T3	62	8.39 (1.48)	9.00 (3)	221	8.16 (1.85)	8.00 (3)		42	7.98 (2.18)	8.00 (3)	218	8.38 (1.71)	9.00 (2)
T4	14	8.50 (1.40)	9.00 (2)	78	8.26 (1.65)	8.00 (3)		13	8.38 (2.93)	10.00 (3)	61	8.72 (1.33)	9.00 (2)
Control – HLA Ab testing													
T1	71	6.86 (2.07)	7.00 (3)	329	6.94 (2.36)	7.00 (4)		66	6.26 (2.54)	6.00 (3)	302	7.14 (2.20)	7.00 (4)
T2	35	7.74 (2.03)	8.00 (3)	148	7.22 (2.13)	8.00 (3)		32	6.50 (2.30)	6.00 (3)	123	7.02 (4)	7.00 (4)
T3	62	7.44 (2.11)	8.00 (3)	218	7.20 (2.25)	8.00 (3)		42	6.71 (1.92)	7.00 (3)	203	7.14 (2.08)	7.00 (3)
T4	14	8.50 (1.74)	9.00 (2)	75	7.65 (1.64)	8.00 (3)		12	8.33 (2.27)	9.00 (2)	58	7.24 (2.01)	8.00 (3)
Concern about risk of transplant failure													
T1	73	7.27 (2.67)	8.00 (5)	338	7.38 (2.88)	8.00 (5)		67	6.75 (3.18)	7.00 (6)	306	7.30 (2.87)	8.00 (5)
T2	34	6.88 (2.80)	7.00 (5)	148	6.91 (3.06)	8.00 (5)		34	6.91 (2.66)	7.00 (4)	127	7.25 (2.87)	8.00 (5)
T3	62	6.97 (2.92)	8.00 (4)	224	7.20 (2.69)	8.00 (5)		42	6.64 (3.14)	8.00 (4)	218	6.83 (2.94)	8.00 (5)
T4	14	8.21 (1.31)	8.00 (2)	78	6.73 (3.15)	7.00 (5)		13	6.92 (3.10)	8.00 (5)	61	5.97 (3.05)	6.00 (6)
Coherence													
T1	73	7.95 (1.94)	8.00 (3)	336	7.76 (2.29)	8.00 (4)		68	8.09 (2.02)	9.00 (3)	305	7.73 (2.29)	8.00 (4)
T2	34	7.68 (2.24)	8.00 (4)	149	8.02 (2.09)	8.00 (3)		33	7.39 (2.22)	8.00 (5)	126	7.68 (2.07)	8.00 (2)
T3	61	8.21 (1.74)	8.00 (3)	224	7.95 (2.03)	8.00 (3)		42	8.19 (1.76)	9.00 (3)	217	7.77 (2.13)	8.00 (2)
T4	14	8.64 (1.22)	8.50 (2)	77	8.14 (1.71)	8.00 (3)		13	7.38 (2.76)	8.00 (5)	61	7.89 (1.90)	8.00 (2)
Emotional Representations													
T1	72	5.01 (3.07)	5.00 (6)	340	5.31 (3.33)	5.00 (6)		67	4.96 (3.35)	5.00 (6)	302	5.56 (3.31)	6.00 (6)
T2	34	5.29 (3.03)	6.00 (6)	147	5.35 (3.15)	6.00 (6)		32	4.97 (2.81)	5.00 (4)	125	5.23 (3.00)	5.00 (5)
T3	61	5.48 (2.88)	6.00 (4)	223	5.18 (3.13)	5.00 (6)		42	4.93 (3.23)	5.00 (6)	216	5.19 (3.09)	5.50 (6)
T4	14	7.14 (1.88)	7.50 (3)	78	5.04 (3.20)	5.00 (6)		13	4.54 (3.33)	4.00 (7)	61	4.41 (2.94)	5.00 (5)

T1: Baseline, T2: 12 months, T3: 24 months, T4: 24-month clock reset data

2. A comparison of post-randomisation adherence to drug therapy and perceptions of risk in the BLC DSA+ and BLC non-DSA+ groups VS. SC DSA+ and SC non-DSA+ groups

Self-reported adherence rates were compared across the AB+ unblinded (BLC) and blinded (SC) groups. No significant differences were seen at any time point.

Table 21 - Comparison of self-reported adherence in the Unblinded (BLC) and Blinded (SC) groups

	AB+ Unblinded (BLC)			AB+ Blinded (SC)			
	n_1	Mean (SD)	Median (IQR)	n_2	Mean (SD)	Median (IQR)	Test result (Mann Whitney U)
MARS Tacrolimus							
T1	281	4.88 (.16)	4.83 (.17)	261	4.86 (.32)	5.00 (.17)	
T2	153	4.87 (.20)	5.00 (.17)	116	4.88 (.20)	5.00 (.17)	*U*: 8448.00, *p*: .46
T3	230	4.86 (.21)	4.83 (.17)	183	4.88 (.14)	4.83 (.17)	*U*: 20620.00, *p*: .70
T4	72	4.88 (.13)	4.83 (.17)	56	4.88 (.18)	4.92 (.17)	*U*: 1938.00, *p*: .68
MARS Mycophenolate							
T1	252	4.89 (.22)	5.00 (.17)	229	4.86 (.34)	5.00 (.17)	
T2	140	4.88 (.22)	5.00 (.17)	119	4.84 (.29)	4.83 (.17)	*U*: 7828.50, *p*: .36
T3	211	4.88 (.19)	5.00 (.17)	173	4.87 (.16)	4.83 (.17)	*U*: 16409.00, *p*: .06
T4	68	4.90 (.12)	4.83 (.17)	49	4.87 (.18)	4.83 (.17)	*U*: 1637.00, *p*: .86
MARS Prednisolone							
T1	210	4.90 (.20)	5.00 (.17)	179	4.90 (.17)	5.00 (.17)	
T2	123	4.86 (.30)	5.00 (.17)	88	4.88 (.22)	5.00 (.17)	*U*: 5378.00, *p*: .93
T3	188	4.89 (.21)	5.00 (.17)	138	4.89 (.14)	5.00 (.17)	*U*: 11946.50, *p*: .17
T4	60	4.89 (.21)	5.00 (.17)	32	4.88 (.11)	4.83 (.17)	*U*: 777.50, *p*: .09

T1: Baseline, T2: 12 months, T3: 24 months, T4: 24-month clock reset data. MARS: Medication Adherence Rating Scale.

Perceptions of risk (B-IPQ) were compared across the AB+ unblinded (BLC) and blinded (SC) groups. No significant differences were seen at any time point.

Table 22 - Comparison of perceptions of risk in the Unblinded (BLC) and Blinded (SC) groups

	Ab+ Unblinded (BLC)			Ab+ Blinded (SC)			
	n_1	Mean (SD)	Median (IQR)	n_2	Mean (SD)	Median (IQR)	Test result
Consequences							

T1	411	6.48 (3.59)	8.00 (7)	373	6.45 (3.56)	8.00 (7)	
T2	184	6.55 (3.39)	8.00 (7)	162	6.79 (3.26)	8.00 (6)	*U*: 14246.00, *p*: .47
T3	286	6.16 (3.44)	7.00 (6)	259	6.28 (3.45)	7.00 (7)	*U*: 36208.50, *p*: .65
T4	92	6.43 (3.41)	8.00 (7)	73	6.34 (3.57)	7.00 (7)	*U*: 3339.50, *p*: .95
Control – Personal							
T1	406	5.94 (2.65)	6.00 (3)	371	5.90 (2.63)	6.00 (3)	
T2	182	5.98 (2.49)	6.00 (3)	157	5.84 (2.41)	6.00 (4)	*U*: 13609.50, *p*: .45
T3	285	6.02 (2.55)	6.00 (3)	258	6.02 (2.35)	6.00 (3)	*U*: 36695.00, *p*: .97
T4	92	6.16 (2.39)	7.00 (3)	74	6.07 (2.28)	7.00 (4)	*U*: 3289.00, *p*: .70
Control – Treatment							
T1	409	8.20 (1.97)	9.00 (2)	372	8.27 (1.82)	8.00 (2)	
T2	181	8.02 (1.73)	8.00 (2)	162	8.34 (1.67)	8.00 (2)	*U*: 12965.00, *p*: .06
T3	283	8.21 (1.78)	8.00 (3)	260	8.32 (1.80)	8.50 (2)	*U*: 35365.00, *p*: .42
T4	92	8.29 (1.61)	8.50 (3)	74	8.66 (1.53)	9.00 (2)	*U*: 2883.50, *p*: .08
Control – HLA Ab testing							
T1	400	6.93 (2.31)	7.00 (4)	368	6.98 (2.28)	7.00 (4)	
T2	183	7.32 (2.12)	8.00 (3)	155	6.91 (2.29)	7.00 (4)	*U*: 12665.50, *p*: .09
T3	280	7.25 (2.22)	8.00 (3)	245	7.07 (2.05)	7.00 (2)	*U*: 31877.50, *p*: .16
T4	89	7.79 (1.68)	8.00 (3)	70	7.43 (2.08)	8.00 (3)	*U*: 2877.50, *p*: .40
Concern about risk of transplant failure							
T1	411	7.36 (2.84)	8.00 (5)	373	7.20 (2.93)	8.00 (5)	
T2	182	6.91 (3.01)	8.00 (5)	161	7.18 (2.82)	8.00 (5)	*U*: 14052.50, *p*: .51
T3	286	7.15 (2.74)	8.00 (5)	260	6.80 (2.97)	8.00 (5)	*U*: 35012.50, *p*: .23
T4	92	6.96 (2.99)	7.00 (5)	74	6.14 (3.06)	6.50 (5)	*U*: 2867.50, *p*: .08
Coherence							
T1	409	7.79 (2.23)	8.00 (3)	373	7.80 (2.24)	8.00 (4)	
T2	183	7.96 (2.11)	8.00 (3)	159	7.62 (2.10)	8.00 (2)	*U*: 12950.50, *p*: .07
T3	285	8.01 (1.98)	8.00 (3)	259	7.84 (2.07)	8.00 (2)	*U*: 35182.50, *p*: .34
T4	91	8.22 (1.65)	8.00 (2)	74	7.80 (2.06)	8.00 (3)	*U*: 3039.00, *p*: .27
Emotional Representation							
T1	412	5.26 (3.28)	5.00 (6)	369	5.45 (3.32)	6.00 (6)	
T2	181	5.34 (3.12)	6.00 (6)	157	5.18 (2.96)	5.00 (5)	*U*: 13723.00, *p*: .59
T3	284	5.25 (3.08)	5.00 (5)	258	5.15 (3.11)	5.00 (6)	*U*: 36148.00, *p*: .79
T4	92	5.36 (3.12)	5.50 (5)	74	4.43 (2.99)	5.00 (5)	*U*: 2857.50, *p*: .07

T1: Baseline, T2: 12 months, T3: 24 months, T4: 24-month clock reset data

Secondary health economics outcomes

There were **173 blinded** and **189 unblinded** HLA positive cases with both baseline and m16 data for costs and QALY. The mean costs in the 12 months prior to baseline (excluding drugs) are **£2287 unblinded** and **£3600 blinded.**The mean costs in the 12 months prior to m16 follow-up (excluding drugs and screening) are **£3137 unblinded** and **£1672 blinded** (so almost a reversal in costs).The cost difference adjusting for baseline is **£1522** (95% CI, -£839 to £3883). So, unblinded care is more expensive but not significantly. Over the 16-month follow-up, the maximum number of QALYs that can be attained is 1.333. The mean QALYs over the 16-month follow-up are **1.0693 for unblinded** and **1.0525 for blinded**. The QALY difference adjusting for baseline quality of life is just **0.0008559** (95% CI, -0.02055 to 0.02226). This is a tiny effect. So, unblinded care costs £1522 more and achieves 0.0008559 more QALYs. The incremental cost-effectiveness ratio is derived by dividing the first number by the second i.e. **£1,778,245 per QALY**. NICE uses a threshold of about £20,000 per QALY and so unblinded care is not cost-effective. Screening costs have not been included. Assuming we would only add these to the unblinded group suggests that cost-effectiveness would be slightly worse.

20.3 Safety results

Provide a summary of the number of subjects that experienced an AE, the total number of AEs and SAEs/SARs/SUSARs. Provide details of any deaths.

Within the per protocol population (which is equivalent to the ITT population for the purpose of this trial) (n= 2035), a total of 8189 AEs, including 670 SAES, were reported in the database and included in the safety analysis. Summary tables for AEs and SAEs are presented in the appendix of this synopsis.

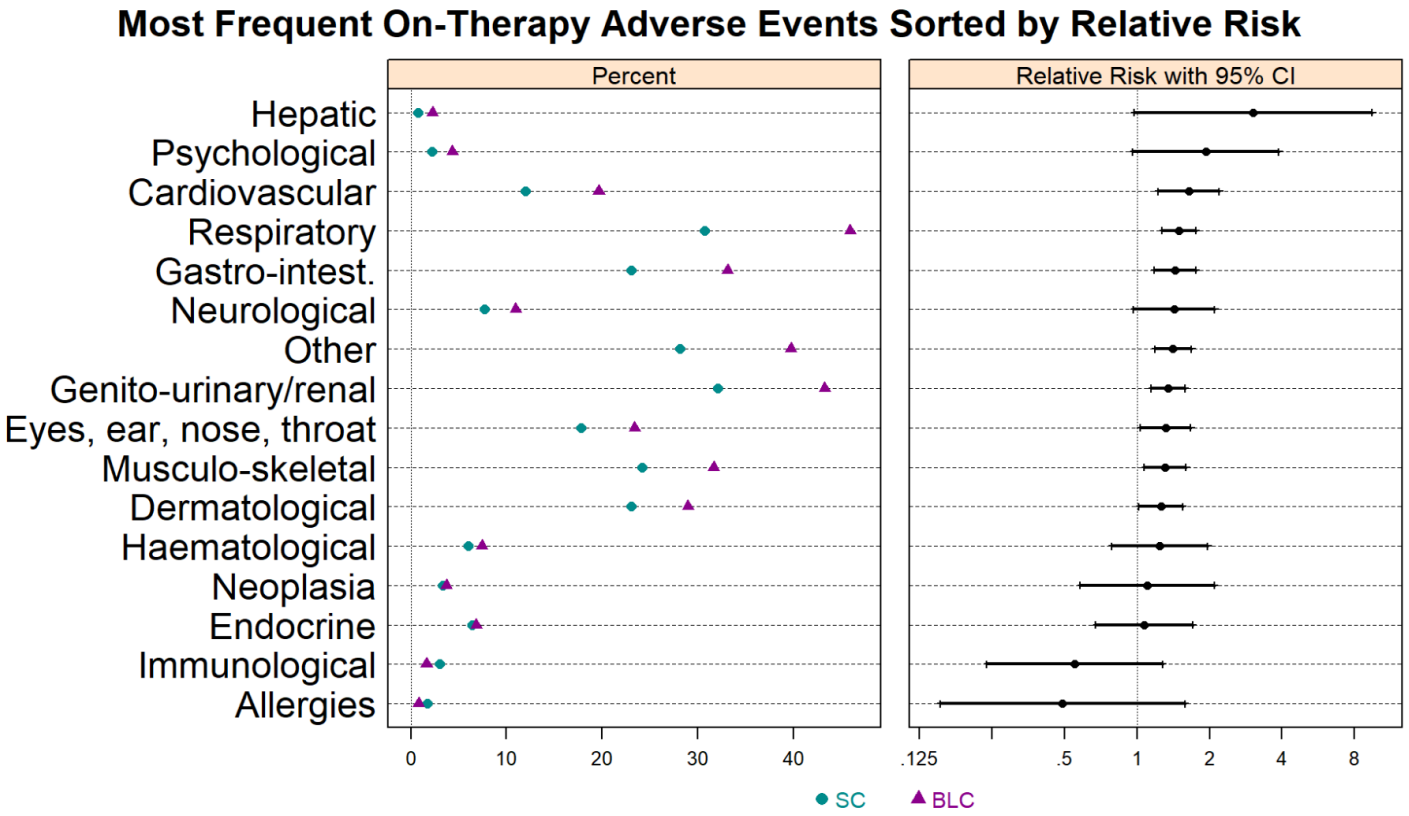
This trial fulfils the criteria for a 'Type A' trial (i.e. risk no higher than that of standard care). Reduced reporting of adverse events to the Sponsor was implemented in a protocol amendment in version 11 of the protocol 26/11/2015. Following this, as stated in the protocol, SAEs were only reported to the sponsor if they:
a) occurred for a participant who was assigned IMP status (i.e. those in the unblinded HLA Ab positive arm who have undergone optimisation)
a) resulted in death
b) required hospitalisations resulting in kidney graft failure
c) were SAR's that would prompt yellow-card reporting in the blinded arm of the trial.

A total of 442 SAEs (13 of which were SARs) were reported to the sponsor.

Overall, 1570 patients (77%) patients experienced at least one AE. The proportion that experienced at least one SAE was 18% (n=375).

The graph below shows the percentage of participants in each arm who experienced an AE in each body system group for HLA Positive participants. Relative risks for BLC/Unblinded arm compared to SC/Blinded are also given with 95% confidence intervals (CI). As such relative risks less than 1 favour the BLC arm, greater than 1 favour the SC arm. There was evidence that participants in the biomarker-led care arm were more likely to experience adverse events across several different body system categories.

Figure 5 - AEs by Body System in HLA Positive participants ordered by size of relative risk



Incidence of adverse drug reactions (ADRs): AEs were only reported as possibly adverse drug reactions in the BLC groups (HLA +ve DSA BLC and HLA +ve non-DSA BLC) as these were the only groups which received IMPs as per trial design and as the trial was open-label (in respect to IMPs). 43 / 2722 (1.5%) adverse events in these groups were assessed as related to at least one study drug and 43/533 patients (8.1%) experienced an ADR. There were 43 Serious Adverse Reactions (SARs) experienced by 27/533 participants (5.1%). No unexpected SARs or SUSARs were reported.

Listing of Serious Adverse Events for all patients

Attached to this report is an Excel file with a listing of all SAEs. ID in the listing is a dummy identifier in order to indicate where multiple SAEs occurred for a participant.

Deaths

Deaths were a secondary outcome, number of deaths by Trial arm/HLA group following re-screening are provided below up until the final ("Post COVID 19") data collection timepoint. As per the secondary outcomes, there was no evidence of a difference in time to death between arms.

DSA BLC	DSA SC	Non-DSA BLC	Non DSA SC	Neg Unblinded	Neg Blinded	Total
6 (5.7%)	3 (3.3%)	37 (8.7%)	28 (7.2%)	52 (10.5%)	50 (9.5%)	176 (8.6%)

20.4 Conclusion

In this large, UK multicentre double-blinded trial we have found no evidence that regular screening for HLA antibodies in patients beyond 1 year post-transplantation, followed by tailored optimisation of immunosuppression impacts on graft failure. More than 95% of the unblinded Ab+ group underwent the optimisation intervention, which included an interview and tailored increases in immunosuppression, and although fewer than 50% of these ended up on triple therapy prednisolone, tacrolimus and MMF, this was twice as many as were on this combination in the blinded group. There was some evidence that the unblinded group suffered fewer biopsy-proven clinical rejection episodes (although not reaching statistical significance at a $p<0.05$ level), and that optimization of immunosuppression was associated with a slightly increased risk of particular types of AEs, suggesting that our intervention may have impacted on expected clinical outcomes. However, graft failure rates in the blinded (control) group were considerably lower than reported in cohorts pre-2010 (as used in the sample size calculations) especially among participants with non-DSA HLA antibodies. It is likely this is due to a higher proportion of patients already taking tacrolimus and MMF compared to pre-2010 cohorts. We conclude that, in the absence of specific and proven interventions to treat DSA, renal transplant recipients on 'modern era' immunosuppression likely do not benefit from regular screening for HLA antibodies followed by interventions based on optimising oral immunosuppression.

21. Date of Report

This is version 1.0 of the Clinical Study Report synopsis, dated 21/12/2021

APPENDICES

i) Summary of all adverse events

Table 23 - Total number and percentage of Adverse Events by HLA status and trial arm

Percentages use the total number of Adverse events as denominator.

	DSA BLC	DSA SC	Non-DSA BLC	Non DSA SC	Neg Unblinded	Neg Blinded	Total
AE	540 (6.6%)	446 (5.4%)	2107 (26%)	1651 (20%)	1498 (18%)	1947 (24%)	8189

Table 24 - Number and percentage of participants who experienced an AE by HLA status and trial arm

Percentages use number of randomised participants in that group as a denominator.

	DSA BLC	DSA SC	Non-DSA BLC	Non DSA SC	Neg Unblinded	Neg Blinded	Total
AE	92 (87%)	68 (73%)	356 (83%)	307 (79%)	352 (71%)	395 (75%)	1570 (77%)

Table 25 - Number of Adverse events by Body system code and HLA status/trial arm

Percentages use the total number of Adverse events within HLA status/trial arm as denominator. NB The coding list used in OuTSMART was from 2012, when it was not a requirement to use MedDra.

Body system code	DSA BLC	DSA SC	Non-DSA BLC	Non DSA SC	Neg Unblinded	Neg Blinded	Total
Allergies	0 (0.0%)	3 (0.7%)	4 (0.2%)	9 (0.5%)	1 (0.1%)	3 (0.2%)	20 (0.2%)
Cardiovascular	25 (4.6%)	5 (1.1%)	110 (5.2%)	79 (4.8%)	78 (5.2%)	89 (4.6%)	386 (4.7%)
Dermatological	49 (9.1%)	38 (8.5%)	188 (8.9%)	162 (9.8%)	115 (7.7%)	145 (7.4%)	697 (8.5%)
Endocrine	7 (1.3%)	6 (1.3%)	28 (1.3%)	34 (2.1%)	21 (1.4%)	40 (2.1%)	136 (1.7%)

Body system code	DSA BLC	DSA SC	Non-DSA BLC	Non DSA SC	Neg Unblinded	Neg Blinded	Total
Eyes, ear, nose, throat	39 (7.2%)	29 (6.5%)	119 (5.6%)	112 (6.8%)	79 (5.3%)	110 (5.6%)	488 (6.0%)
Gastro-intest.	48 (8.9%)	45 (10%)	225 (11%)	152 (9.2%)	174 (12%)	198 (10%)	842 (10%)
Genito-urinary/renal	129 (24%)	72 (16%)	387 (18%)	333 (20%)	287 (19%)	377 (19%)	1585 (19%)
Haematological	9 (1.7%)	9 (2.0%)	38 (1.8%)	32 (1.9%)	29 (1.9%)	39 (2.0%)	156 (1.9%)
Hepatic	3 (0.6%)	2 (0.4%)	23 (1.1%)	2 (0.1%)	9 (0.6%)	5 (0.3%)	44 (0.5%)
Immunological	2 (0.4%)	4 (0.9%)	9 (0.4%)	14 (0.8%)	4 (0.3%)	10 (0.5%)	43 (0.5%)
Musculo-skeletal	50 (9.3%)	52 (12%)	209 (9.9%)	165 (10%)	160 (11%)	215 (11%)	851 (10%)
Neoplasia	1 (0.2%)	3 (0.7%)	25 (1.2%)	21 (1.3%)	10 (0.7%)	16 (0.8%)	76 (0.9%)
Neurological	12 (2.2%)	17 (3.8%)	54 (2.6%)	35 (2.1%)	42 (2.8%)	39 (2.0%)	199 (2.4%)
Other	79 (15%)	82 (18%)	318 (15%)	243 (15%)	210 (14%)	302 (16%)	1234 (15%)
Psychological	3 (0.6%)	2 (0.4%)	20 (0.9%)	12 (0.7%)	13 (0.9%)	26 (1.3%)	76 (0.9%)
Respiratory	84 (16%)	77 (17%)	350 (17%)	246 (15%)	266 (18%)	333 (17%)	1356 (17%)

Table 26 - Number of participants with an adverse event by body system code and HLA status/trial arm

Percentages use number of randomised participants in that group as a denominator

Body system	DSA BLC	DSA SC	Non-DSA BLC	Non DSA SC	Neg Unblinded	Neg Blinded	Total
Allergies	0 (0.0%)	1 (1.1%)	4 (0.9%)	8 (2.0%)	1 (0.2%)	3 (0.6%)	17 (0.8%)
Cardiovascular	15 (14.2%)	4 (4.3%)	80 (18.7%)	60 (15.3%)	57 (11.5%)	66 (12.5%)	282 (13.8%)
Dermatological	27 (25.5%)	24 (26.1%)	113 (26.5%)	99 (25.3%)	76 (15.4%)	101 (19.2%)	440 (21.6%)
Endocrine	7 (6.6%)	6 (6.5%)	26 (6.1%)	28 (7.2%)	21 (4.2%)	29 (5.5%)	117 (5.7%)
Eyes, ear, nose, throat	24 (22.6%)	19 (20.7%)	89 (20.8%)	76 (19.4%)	59 (11.9%)	82 (15.6%)	349 (17.1%)
Gastro-intest.	32 (30.2%)	29 (31.5%)	128 (30.0%)	94 (24.0%)	105 (21.2%)	116 (22.1%)	504 (24.7%)
Genito-urinary/renal	46 (43.4%)	30 (32.6%)	163 (38.2%)	141 (36.1%)	130 (26.3%)	163 (31.0%)	673 (33.0%)
Haematological	7 (6.6%)	7 (7.6%)	29 (6.8%)	25 (6.4%)	26 (5.3%)	35 (6.7%)	129 (6.3%)
Hepatic	2 (1.9%)	2 (2.2%)	9 (2.1%)	2 (0.5%)	6 (1.2%)	4 (0.8%)	25 (1.2%)

Immunological	1 (0.9%)	3 (3.3%)	7 (1.6%)	13 (3.3%)	4 (0.8%)	9 (1.7%)	37 (1.8%)
Musculo-skeletal	32 (30.2%)	26 (28.3%)	121 (28.3%)	103 (26.3%)	106 (21.4%)	134 (25.5%)	522 (25.6%)
Neoplasia	1 (0.9%)	2 (2.2%)	17 (4.0%)	16 (4.1%)	9 (1.8%)	9 (1.7%)	54 (2.7%)
Neurological	10 (9.4%)	12 (13.0%)	43 (10.1%)	29 (7.4%)	30 (6.1%)	31 (5.9%)	155 (7.6%)
Other	35 (33.0%)	34 (37.0%)	157 (36.8%)	116 (29.7%)	118 (23.8%)	150 (28.5%)	610 (29.9%)
Psychological	3 (2.8%)	2 (2.2%)	18 (4.2%)	10 (2.6%)	11 (2.2%)	23 (4.4%)	67 (3.3%)
Respiratory	46 (43.4%)	37 (40.2%)	176 (41.2%)	127 (32.5%)	149 (30.1%)	177 (33.7%)	712 (35.0%)

ii) Summary of treatment-emergent ARs in the per protocol population

AEs were only reported as possibly adverse drug reactions in the BLC groups (HLA +ve DSA BLC and HLA +ve non-DSA BLC) as these were the only groups which received IMP as per trial design.

Table 27 - Number of ARs by Body System Code (BLC groups only)

Percentages are as percentages of total number of ARs within group.

Body System Code	1. DSA BLC	3. Non-DSA BLC	Total
Allergies	0 (-)	0 (-)	0 (-)
Cardiovascular	4 (3.2%)	18 (3.1%)	22 (3.1%)
Dermatological	21 (16.7%)	72 (12.4%)	93 (13.2%)
Endocrine	3 (2.4%)	15 (2.6%)	18 (2.6%)
Eyes, ear, nose, throat	7 (5.6%)	30 (5.2%)	37 (5.2%)
Gastro-intest.	12 (9.5%)	73 (12.6%)	85 (12.1%)
Genito-urinary/renal	26 (20.6%)	129 (22.3%)	155 (22.0%)
Haematological	3 (2.4%)	11 (1.9%)	14 (2.0%)
Hepatic	3 (2.4%)	4 (0.7%)	7 (1.0%)
Immunological	2 (1.6%)	5 (0.9%)	7 (1.0%)
Musculo-skeletal	9 (7.1%)	14 (2.4%)	23 (3.3%)
Neoplasia	1 (0.8%)	17 (2.9%)	18 (2.6%)
Neurological	0 (-)	20 (3.5%)	20 (2.8%)
Other	14 (11.1%)	45 (7.8%)	59 (8.4%)

Body System Code	1. DSA BLC	3. Non-DSA BLC	Total
Psychological	0 (-)	8 (1.4%)	8 (1.1%)
Respiratory	21 (16.7%)	118 (20.4%)	139 (19.7%)

iii) Summary of treatment-emergent SAEs in the study population

Table 28 - Total number and percentage of Serious Adverse Events by HLA status and trial arm

Percentages are percentages out of all reported SAEs.

	DSA BLC	DSA SC	Non-DSA BLC	Non DSA SC	Neg Unblinded	Neg Blinded	Total
SAE	65 (10%)	33 (4.9%)	164 (24%)	104 (16%)	135 (20%)	169 (25%)	670

Table 29 - Number and percentage of participants experienced an SAEs by HLA status and trial arm

Percentages are percentages of all randomised participants in those groups

	DSA BLC	DSA SC	Non-DSA BLC	Non DSA SC	Neg Unblinded	Neg Blinded	Total
SAE	26 (25%)	18 (20%)	93 (22%)	65 (17%)	85 (17%)	88 (17%)	375 (18%)

Table 30 - Number of SAES by group and Body system code

Body system code	1. DSA BLC	2. DSA SC	3. Non-DSA BLC	4. Non DSA SC	5. Neg Unblinded	6. Neg Blinded	Total
Allergies	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)
Cardiovascular	8 (12.3%)	0 (-)	16 (9.8%)	6 (5.8%)	17 (12.7%)	8 (4.7%)	55 (8.2%)
Dermatological	1 (1.5%)	0 (-)	3 (1.8%)	3 (2.9%)	3 (2.2%)	5 (3.0%)	15 (2.2%)
Endocrine	1 (1.5%)	0 (-)	3 (1.8%)	4 (3.8%)	4 (3.0%)	0 (-)	12 (1.8%)
Eyes, ear, nose, throat	0 (-)	1 (3.0%)	2 (1.2%)	2 (1.9%)	0 (-)	0 (-)	5 (0.7%)
Gastro-intest.	9 (13.8%)	5 (15.2%)	16 (9.8%)	10 (9.6%)	20 (14.9%)	35 (20.7%)	95 (14.2%)
Genito-urinary/renal	29 (44.6%)	17 (51.5%)	53 (32.3%)	37 (35.6%)	44 (32.8%)	51 (30.2%)	231 (34.5%)
Haematological	2 (3.1%)	3 (9.1%)	3 (1.8%)	3 (2.9%)	4 (3.0%)	6 (3.6%)	21 (3.1%)
Hepatic	0 (-)	0 (-)	9 (5.5%)	0 (-)	2 (1.5%)	2 (1.2%)	13 (1.9%)
Immunological	0 (-)	0 (-)	1 (0.6%)	0 (-)	0 (-)	0 (-)	1 (0.1%)
Musculo-skeletal	1 (1.5%)	2 (6.1%)	7 (4.3%)	2 (1.9%)	6 (4.5%)	6 (3.6%)	24 (3.6%)
Neoplasia	1 (1.5%)	0 (-)	3 (1.8%)	0 (-)	1 (0.7%)	2 (1.2%)	7 (1.0%)
Neurological	1 (1.5%)	0 (-)	3 (1.8%)	2 (1.9%)	3 (2.2%)	4 (2.4%)	13 (1.9%)
Other	6 (9.2%)	3 (9.1%)	30 (18.3%)	20 (19.2%)	18 (13.4%)	26 (15.4%)	103 (15.4%)

Body system code	1. DSA BLC	2. DSA SC	3. Non-DSA BLC	4. Non DSA SC	5. Neg Unblinded	6. Neg Blinded	Total
Psychological	0 (-)	0 (-)	0 (-)	2 (1.9%)	0 (-)	0 (-)	2 (0.3%)
Respiratory	6 (9.2%)	2 (6.1%)	15 (9.1%)	13 (12.5%)	12 (9.0%)	24 (14.2%)	72 (10.8%)

Table 31 - Number of participants with an SAE by group and Body system code

Body system code	1. DSA BLC	2. DSA SC	3. Non-DSA BLC	4. Non DSA SC	5. Neg Unblinded	6. Neg Blinded	Total
Allergies	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)
Cardiovascular	4 (9.8%)	0 (-)	13 (10.2%)	6 (7.1%)	14 (13.1%)	6 (4.8%)	43 (8.4%)
Dermatological	1 (2.4%)	0 (-)	3 (2.3%)	3 (3.5%)	3 (2.8%)	5 (4.0%)	15 (2.9%)
Endocrine	1 (2.4%)	0 (-)	3 (2.3%)	4 (4.7%)	4 (3.7%)	0 (-)	12 (2.3%)
Eyes, ear, nose, throat	0 (-)	1 (3.7%)	2 (1.6%)	2 (2.4%)	0 (-)	0 (-)	5 (1.0%)
Gastro-intest.	6 (14.6%)	5 (18.5%)	14 (10.9%)	10 (11.8%)	16 (15.0%)	26 (21.0%)	77 (15.0%)
Genito-urinary/renal	14 (34.1%)	11 (40.7%)	38 (29.7%)	23 (27.1%)	29 (27.1%)	31 (25.0%)	146 (28.5%)
Haematological	2 (4.9%)	3 (11.1%)	1 (0.8%)	2 (2.4%)	4 (3.7%)	5 (4.0%)	17 (3.3%)
Hepatic	0 (-)	0 (-)	3 (2.3%)	0 (-)	1 (0.9%)	1 (0.8%)	5 (1.0%)
Immunological	0 (-)	0 (-)	1 (0.8%)	0 (-)	0 (-)	0 (-)	1 (0.2%)
Musculo-skeletal	1 (2.4%)	2 (7.4%)	6 (4.7%)	2 (2.4%)	6 (5.6%)	5 (4.0%)	22 (4.3%)
Neoplasia	1 (2.4%)	0 (-)	3 (2.3%)	0 (-)	1 (0.9%)	1 (0.8%)	6 (1.2%)
Neurological	1 (2.4%)	0 (-)	3 (2.3%)	2 (2.4%)	3 (2.8%)	4 (3.2%)	13 (2.5%)
Other	5 (12.2%)	3 (11.1%)	25 (19.5%)	17 (20.0%)	15 (14.0%)	23 (18.5%)	88 (17.2%)
Psychological	0 (-)	0 (-)	0 (-)	2 (2.4%)	0 (-)	0 (-)	2 (0.4%)
Respiratory	5 (12.2%)	2 (7.4%)	13 (10.2%)	12 (14.1%)	11 (10.3%)	17 (13.7%)	60 (11.7%)

iv) Summary of treatment-emergent SARs in the study population

Table 32 - Number of SARs by Body System Code and Group

Body System Code	1. DSA BLC	3. Non-DSA BLC	Total

Allergies	0 (-)	0 (-)	0 (-)
Cardiovascular	3 (25.0%)	0 (-)	3 (7.0%)
Dermatological	0 (-)	3 (9.7%)	3 (7.0%)
Endocrine	0 (-)	0 (-)	0 (-)
Eyes, ear, nose, throat	0 (-)	0 (-)	0 (-)
Gastro-intest.	1 (8.3%)	2 (6.5%)	3 (7.0%)
Genito-urinary/renal	3 (25.0%)	14 (45.2%)	17 (39.5%)
Haematological	1 (8.3%)	1 (3.2%)	2 (4.7%)
Hepatic	0 (-)	0 (-)	0 (-)
Immunological	0 (-)	0 (-)	0 (-)
Musculo-skeletal	0 (-)	0 (-)	0 (-)
Neoplasia	1 (8.3%)	1 (3.2%)	2 (4.7%)
Neurological	0 (-)	0 (-)	0 (-)
Other	2 (16.7%)	5 (16.1%)	7 (16.3%)
Psychological	0 (-)	0 (-)	0 (-)
Respiratory	1 (8.3%)	5 (16.1%)	6 (14.0%)

Listing of SARs (BLC groups only)

The BLC groups were the only groups to receive IMP and therefore only groups which could have SARs.

Table 33 - Listing of all SARs

ID	Description	Body System Code	Related to Study Drug?	Group
1	Metastatic malignant disease	Other	3. Possibly	3. Non-DSA BLC
2	Acute kidney dysfunction	Genito-urinary/renal	3. Possibly	3. Non-DSA BLC
3	Metastatic Renal Cell Carcinoma	Neoplasia	3. Possibly	1. DSA BLC
4	Squamous cell carcinoma	Dermatological	3. Possibly	3. Non-DSA BLC
5	Pneumonia	Respiratory	3. Possibly	3. Non-DSA BLC
5	Acute kidney injury	Genito-urinary/renal	3. Possibly	3. Non-DSA BLC
6	Query viral illness	Other	3. Possibly	3. Non-DSA BLC
7	severe sepsis & multi-organ failure	Other	3. Possibly	1. DSA BLC
8	transplant pyelonephritis	Genito-urinary/renal	3. Possibly	3. Non-DSA BLC
8	transplant pyelonephritis	Genito-urinary/renal	3. Possibly	3. Non-DSA BLC
8	transplant pyelonephritis	Genito-urinary/renal	3. Possibly	3. Non-DSA BLC
9	Chest infection	Respiratory	2. Likely	1. DSA BLC
9	transplant pyelonephritis	Genito-urinary/renal	2. Likely	1. DSA BLC
9	3episodes of UTI (E.coli)	Genito-urinary/renal	2. Likely	1. DSA BLC
9	pyelonephritis	Genito-urinary/renal	3. Possibly	1. DSA BLC
10	PTLD	Other	3. Possibly	1. DSA BLC
11	Shortness of breath	Cardiovascular	3. Possibly	1. DSA BLC
11	chest pain/heart failure	Cardiovascular	3. Possibly	1. DSA BLC
11	hypertensive	Cardiovascular	3. Possibly	1. DSA BLC
11	Diarrhoea	Gastro-intestinal	3. Possibly	1. DSA BLC
12	Pneumocystis infection	Respiratory	3. Possibly	3. Non-DSA BLC
12	Hepatocellular carcinoma, patient died	Neoplasia	3. Possibly	3. Non-DSA BLC
13	Alopecia universalis	Dermatological	3. Possibly	3. Non-DSA BLC

ID	Description	Body System Code	Related to Study Drug?	Group
14	Admitted to Tameside with neitropenia and sepsis	Haematological	3. Possibly	1. DSA BLC
15	Admitted with acute viral illness	Other	3. Possibly	3. Non-DSA BLC
15	Admitted with Klebsiella UTI	Genito-urinary/renal	3. Possibly	3. Non-DSA BLC
15	Admitted with CMV viraemia	Haematological	3. Possibly	3. Non-DSA BLC
15	Admitted with graft dysfunction	Genito-urinary/renal	3. Possibly	3. Non-DSA BLC
16	Acute Gastroenteritis secondary Campylobacter Infection	Gastro-intestinal	3. Possibly	3. Non-DSA BLC
17	left sided pneumonia	Respiratory	1. Definitely	3. Non-DSA BLC
18	UTI	Genito-urinary/renal	3. Possibly	3. Non-DSA BLC
19	Biopsy	Other	3. Possibly	3. Non-DSA BLC
20	UTI - septicaemia	Genito-urinary/renal	3. Possibly	3. Non-DSA BLC
21	Skin Currettings Left Upper Back	Dermatological	2. Likely	3. Non-DSA BLC
22	abdominal pain	Gastro-intestinal	2. Likely	3. Non-DSA BLC
23	Urinary Tract Infection	Genito-urinary/renal	2. Likely	3. Non-DSA BLC
24	Graft pyelonephritis	Genito-urinary/renal	2. Likely	3. Non-DSA BLC
24	Urinary Tract Infection	Genito-urinary/renal	2. Likely	3. Non-DSA BLC
24	Urinary Tract Infection	Genito-urinary/renal	2. Likely	3. Non-DSA BLC
25	urosepsis	Genito-urinary/renal	2. Likely	3. Non-DSA BLC
25	lower respiratory tract infection	Respiratory	2. Likely	3. Non-DSA BLC
26	ovarian cyst	Other	3. Possibly	3. Non-DSA BLC
27	bacteremia	Respiratory	3. Possibly	3. Non-DSA BLC