# RISK FACTORS FOR ACUTE ALLOGRAFT REJECTION IN HIV+ KIDNEY TRANSPLANT RECIPIENTS

E GATHOGO[1,2], M HARBER[2], S BHAGANI[2], J BAXTER[3], J LEIGHTON[3], V LEE[3], J LEVY[4], R JONES[5], R HILTON[6], G DAVIES[1], F POST[7] ON BEHALF OF THE UK HIV KIDNEY TRANSPLANT STUDY GROUP

[1]KING'S COLLEGE LONDON, [2]ROYAL FREE LONDON NHS FOUNDATION TRUST, [3]CENTRAL MANCHESTER UNIVERSITY HOSPITALS, [4]IMPERIAL COLLEGE HEALTHCARE NHS TRUST, LONDON, [5]CHELSEA AND WESTMINSTER HOSPITAL, LONDON, [6]GUY'S AND ST THOMAS' NHS FOUNDATION TRUST, LONDON, [7]KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST


**Departments of Pharmacy & HIV Medicine**

Royal Free London NHS Foundation Trust

**Faculty of Life Sciences & Medicine**
Transplantation Immunology & Muscosal Biology
Department of Renal Sciences

KING'S College LONDON

# Background

- Kidney transplantation (KT) of HIV positive patients has transformed the management of end-stage kidney disease.
- Excellent patient and graft survival albeit, high rates of acute allograft rejection (AR).
- We examined factors associated with AR in the first year post-KT, with particular emphasis on the choice of calcineurin inhibitor (CNI) immunosuppressive therapy.

# Methods

- Observational cohort study including 40 Transplant and HIV referring centres in the UK
- NHS MREC and local R&D approval
- Inclusion: all HIV+ patients ≥ 18 years of age transplanted in the UK between 01/01/2005 – 31/12/2014
- Exclusion: patients transplanted abroad, KT recipients that acquired HIV post-KT; age < 18 years; no data available
- Survival analyses & cumulative incidence of BPAR was estimated using Kaplan-Meier methods;
- Cox-proportional hazard regression analyses were used to identify factors associated with BPAR

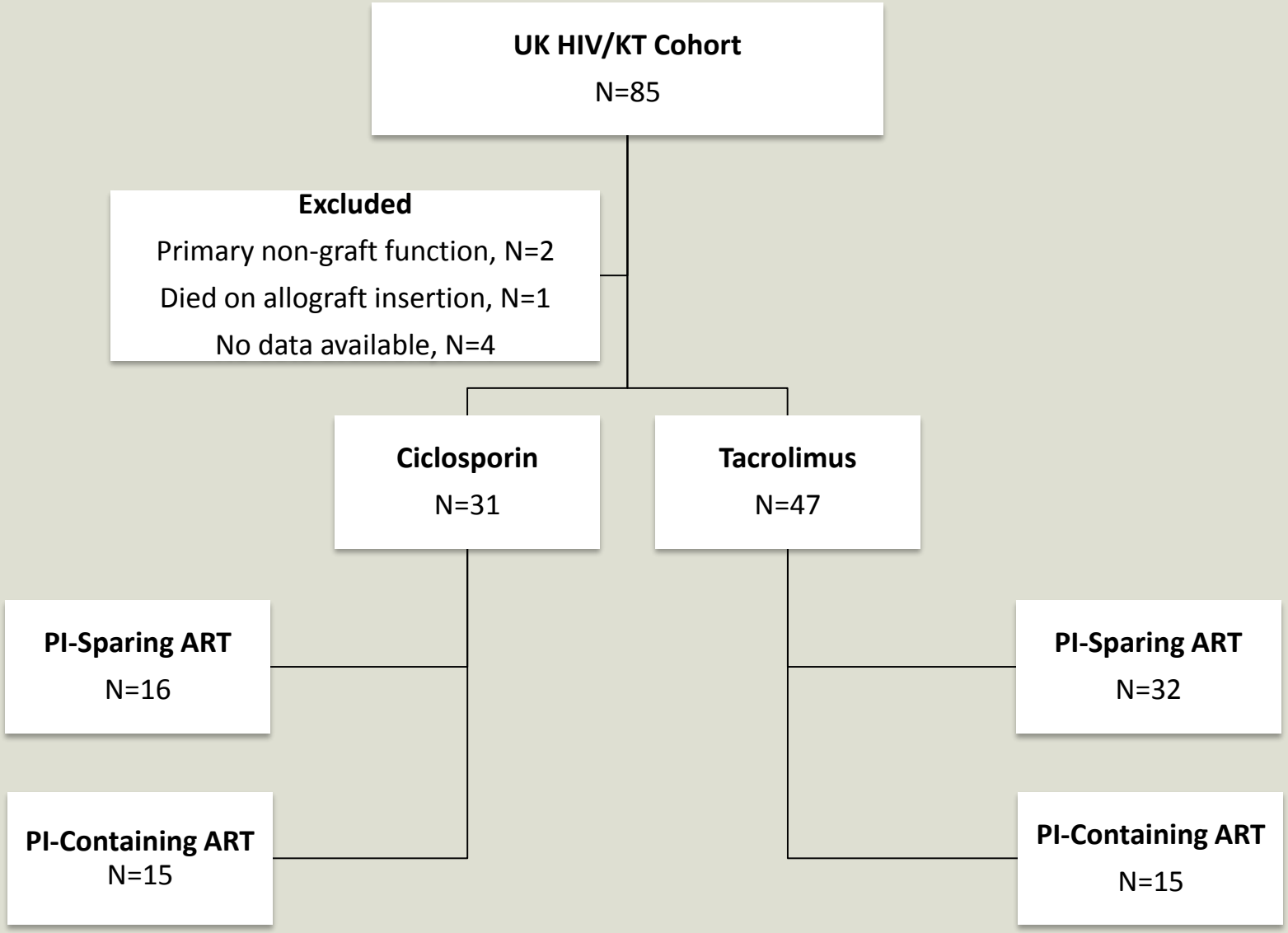
# Overall Outcomes

- N=85 patients received a kidney allograft
  - Living donor 27 (33%)
  - Deceased donor 56 (67%)

- Patient survival at 1, 2 and 5 years post KT:
  - 98%, 98% and 88% (our cohort)
  - 96-99%, 91-98% and 85-95% (general KT population)

- Graft survival at 1, 2 and 5 years post KT:
  - 98%, 96% and 77% (our cohort)
  - 92-97%, 91-95%, 85-91% (general KT population)

# Patient Disposition



# Baseline Characteristics

| | | Ciclosporin | Tacrolimus | P |
|---|---|---|---|---|
| **N** | | **31** | **47** | |
| **Age, median (IQR)** | Years | 39.5 (36.6, 49.6) | 47.3 (42.0, 52.6) | **0.01** |
| **Gender, n (%)** | Male | 24 (77) | 28 (60) | 0.10 |
| **Ethnicity, n (%)** | Black | 24 (77) | 34 (72) | 0.62 |
| **Cause of ESKD, n (%) **** | HIVAN | 18 (58) | 22 (48) | 0.38 |
| **Duration of pRRT, median(IQR) ǂ** | Years | 4.5 (2.2, 6.4) | 6.1 (3.3,7.3) | 0.27 |
| **Mode of acquisitionɬ, n (%)** | HTS | 22 (71) | 32 (78) | 0.46 |
| **CD4 count at KT, median (IQR)**** | cells/$mm^3$ | 92 (38, 160) | 95 (41, 179) | 0.93 |
| **Viral load at KT, median (IQR)** | $log_{10}$ copies/ml | 1.7 (1.6, 1.7) | 1.6 (1.6, 1.7) | 0.07 |
| **Hepatitis B co-infection, n (%)**** | sAg positive | 5 (16) | 5 (11) | 0.50 |
| **Hepatitis C co-infection, n (%) ¶** | RNA positive | 3 (10) | 1 (2) | 0.16 |
| **Allograft type, n (%)**** | Cadaveric | 18 (58) | 33 (72) | 0.21 |
| **Donor/Recipient CMV mismatch status, n (%)** | | 2 (6) | 2 (4) | 0.67 |

*Comparing medians, Wilcoxon rank-sum (Mann-Whitney) test; comparing proportions (%), chi-squared test and two-sample test of proportions. Statistically significant ($p < 0.05$); Missing values - **n=1, ¶ n=3, ɬ n=6, ǂ n=7.

Key: IS – immunosuppression, KT – Kidney transplantation, HTS – heterosexual, PI/r – Ritonavir boosted protease inhibitors, CMV – Cytomegalovirus, pRRT – Permanent renal replacement therapy, ESKD – End-stage kidney disease

# Allograft Rejection

- Biopsy proven acute allograft rejection (BPAR) was diagnosed in 28 (36%) patients. Median time to AR was 2.6 (0.5, 5.9) months from allograft insertion.
- Cumulative incidence of BPAR at 1 year: 36.4% vs. 31% USA [1].

**Fig 1A. Time to First Rejection, UK (n=78)**

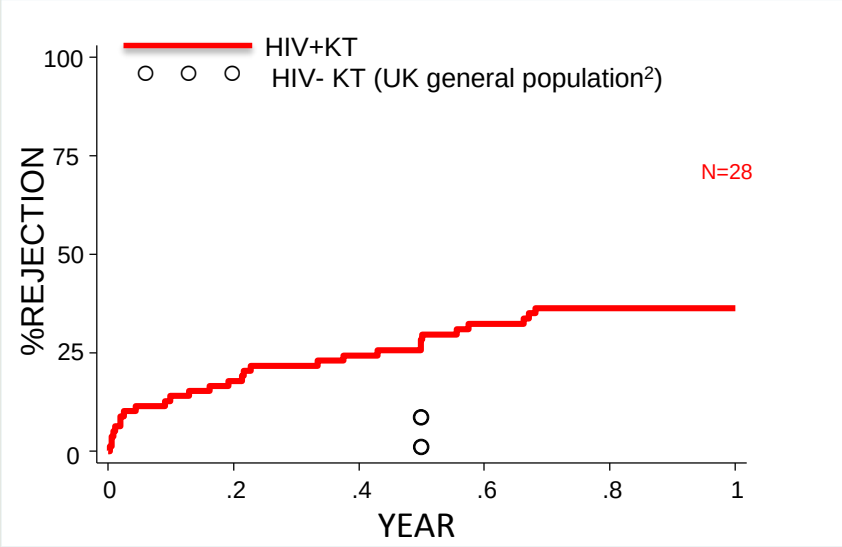
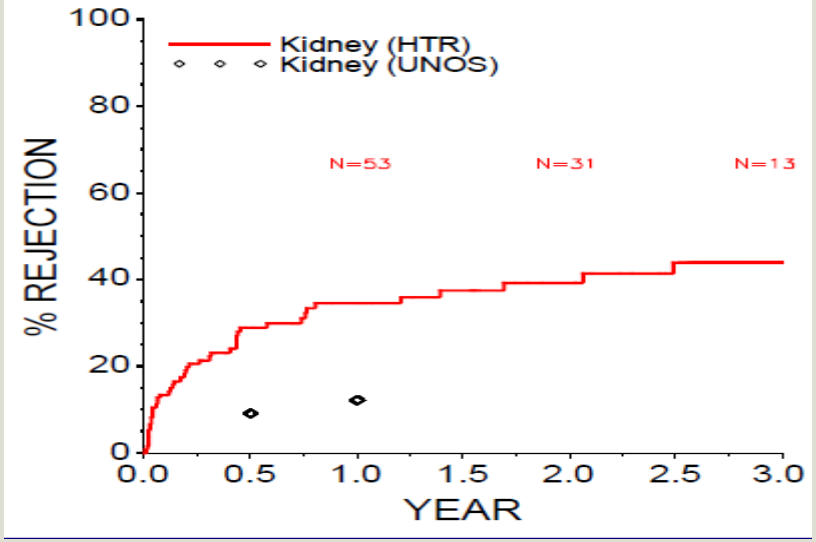


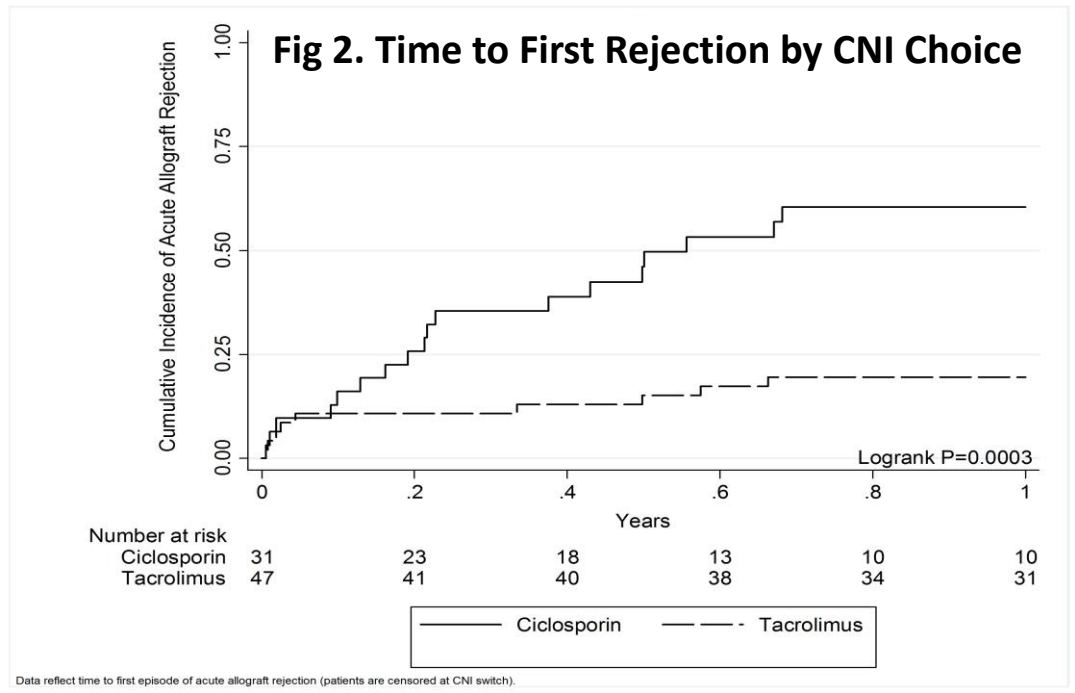

**Fig 1B. Time to First Rejection, USA (n=150)**




1. Stock et al. Outcomes of Kidney transplantation in HIV Infected Recipients. NEJM 2010, 363(21) p.2004-2014
2. The 3C Study Collaborative Group. Alemtuzumab-based induction treatment versus basiliximab-based induction treatment in kidney transplantation (the 3C Study): a randomised trial. Lancet 2014, 384 (9955) p.1684-1690.

# Allograft Rejection by CNI Choice

- BPAR was significantly more common among patients who started CsA (n=18, 58%) compared with Tac (n=10, 21%) [Fig 2]
- ~50% of Tac BPARs occurred within first 14 days
- 12/18 patients on CsA switched to Tac after rejection episode



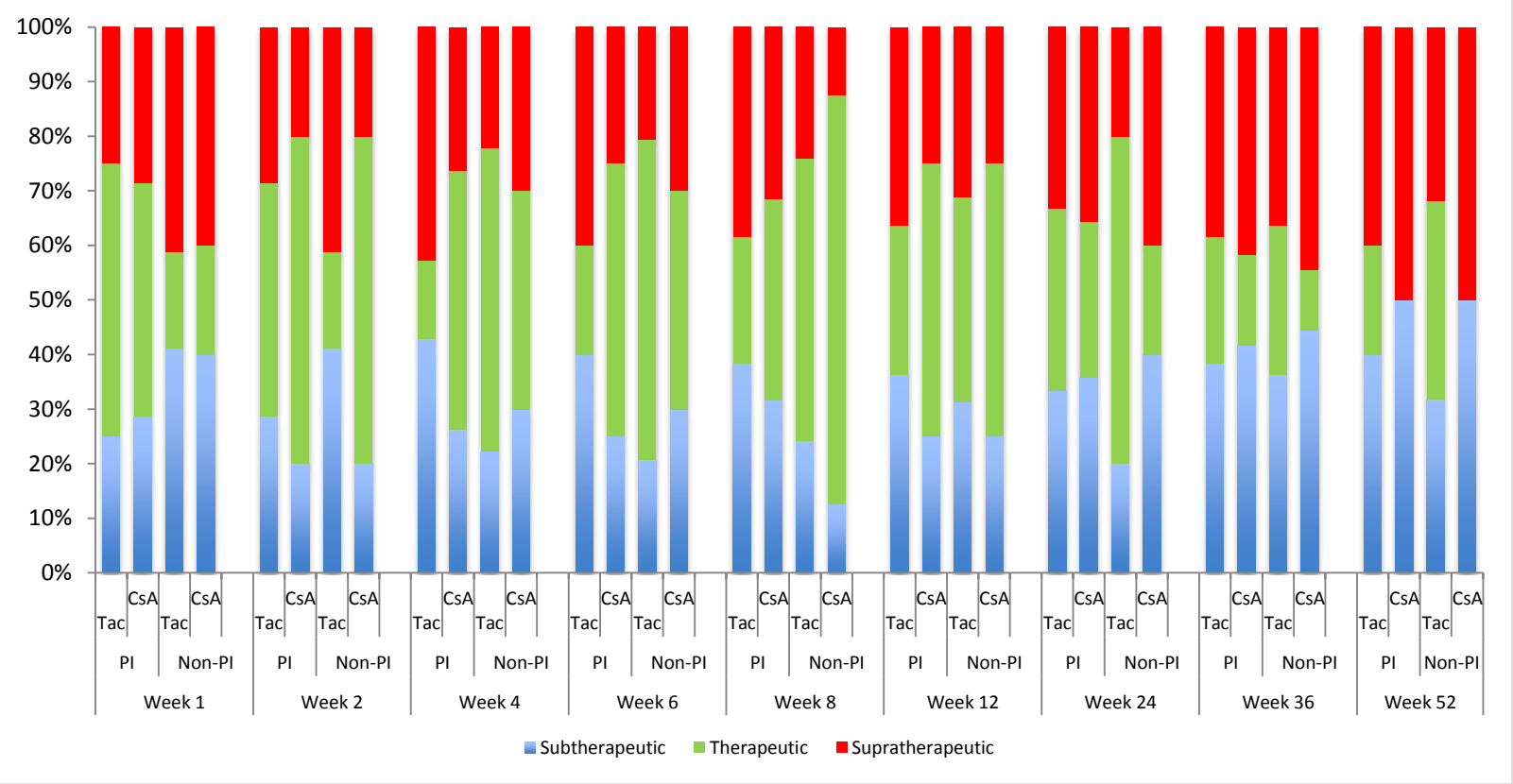
# Factors Associated with BPAR

| | | Univariable HR (95% CI) | P | Multivariable HR (95% CI) | P |
|---|---|---|---|---|---|
| Age at KT (per year older) | | 0.99 (0.94, 1.05) | 0.71 | | |
| cART regimen | PI/r<br>Other | 2.63 (1.08, 6.44)<br>1.00 | **0.03** | 1.06 (0.47, 2.39)<br>1.00 | 0.89 |
| Abacavir containing cART | Yes<br>No | 0.39 (0.16, 0.94)<br>1.00 | **0.04** | 0.74 (0.33, 1.67)<br>1.00 | 0.47 |
| CNI Choice at KT | CsA<br>Tac | 1.00<br>0.16 (0.06, 0.43) | **0.000** | 1.00<br>0.27 (0.12, 0.61) | **0.002** |

HR= Hazard Ratio; 95 % CI= 95% Confidence Interval; P=p-value; Sensitivity – Excluding rejection episodes (N=6) first 14 days (immunological responses)

Other factors considered were gender, ethnicity, mode of HIV acquisition, transplant year, CD4 at KT, HBV, HCV, allograft type, induction and DGF

# Calcineurin $C_{trough}$ Concentrations




- Sub and supra therapeutic concentrations were common irrespective of (1) choice of CNI and (2) inclusion of PI in the cART regimen

# Infectious and Neoplastic Complications

| Ciclosporin | Tacrolimus |
|---|---|
| **HIV Viral Load** | |
| • Viral load blips (50 – 139 cps/mL) [n=4] | HIV VL control in all patients (<50 cps/mL) |
| **Tumour/Neoplasms** | |
| • Kaposi's sarcoma (n=2)<br>• Bowen's disease (n=1)<br>• Melanoma (n=1) | • Basal cell carcinoma (n=1)<br>• Bowen's disease (n=1) |
| **Latent Viral Reactivation (LVR)** | |
| **N=22** | **N=12** |
| • LVR preceding allograft rejection (n=9) | • LVR preceding allograft rejection (n=1) |
| • CMV Infection (n=13)<br>  • CMV prophylaxis (n=9) | • CMV Infection (n=7)<br>  • CMV prophylaxis (n=23) |
| • Herpes simplex (n=4) | Herpes simplex (n=2) |
| • Epstein-Barr Virus (n=0) | Epstein-Barr Virus (n=2) |
| • BK viraemia/nephropathy (n=5) | BK viraemia/nephropathy (n=1) |

# Post-KT Allograft Function


- Median eGFR for AR vs no AR at 1 year (38 [27, 48] vs. 60 [47, 83] mL/min per 1.73 m² (p=0.0002).
- 5 year cumulative incidence of Stage 4/5 CKD in patients who experienced AR at 1 year (42.3% vs. 2.9%, p=0.01)

# Conclusion

- Overall patient survival and graft survival are excellent and comparable to the general KT population

- Patients who experienced BPAR had significantly poorer graft function (eGFR at 1 year and cumulative incidence of stage 4/5 CKD)

- Use of Tac was associated with a significantly reduced incidence of AR in the first year post KT, suggesting that Tac may be the preferred CNI for KT in HIV infection.

# Acknowledgements

**Kings College London**
Graham Davies (School of Biomedical & Health Sciences, Pharmaceutical Science Research Division); Lisa Hamzah; Sophie Jose; and Frank Post

***The UK HIV Kidney Study Group:*** **King's College Hospital NHS Foundation Trust / King's College London** Lisa Hamzah, Bavithra Nathan, Lucy Campbell, Frank Post, Bruce Hendry, Iain MacDougall, Shema Doshi, Mee-Onn Chai, Graham Davies; **Guy's and St Thomas' NHS Foundation Trust** Rachel Hilton, Partha Das, Nick Larbalestier, Lucy Galloway, Hayley Wells, Martin Drage, Linda Ross; **Brighton and Sussex University Hospitals NHS Trust** Debbie Williams, Yvonne Gilleece, Edward Kingdon, Heather Leake Date; **Medway NHS Foundation Trust** Chula Wijesurendra; **Maidstone and Tunbridge Wells NHS Trust** BarbaraVonau; **Barts Health NHS Trust** Hamish Dobbie,Maurice Murphy; **St George's Healthcare Trust and St George's, University of London** Tariq Sadiq, Iain MacPhee, Aseel Hegazi, Joyce Popoola, Philip Hay; **Royal Free London NHS Foundation Trust / University College London** Esther Gathogo, Neal Marshall, Caroline Sabine, Mark Harber, Sanjay Bhagani, Bimbi Fernando, Caroline Ashley, John Farrell, Wendy Spicer, Meera Thacker, Helen Atkinson, Leonie Swaden, Paul Sweny, Alexander Howie, John Connolly, Sabine Kinloch, Margaret Johnson; **Mortimer Market Centre, UCLH** Ian Williams, June Minton; **North Middlesex University Hospital NHS Trust** Chinyere Okoli, Jonathan Ainsworth; **Imperial College Healthcare NHS trust** Jeremy Levy, Nicola Mackie, Alan Winston, Neill Duncan, Dawn Goodall, Rachna Bedi, Nicola Morley; **Chelsea and Westminster NHS Foundation Trust** Rachael Jones, Marta Boffito, Michael Rayment; **North West London Hospitals NHS Trust** Gary Brook, Andrew Shaw, Bhairvi Gosrani; **Oxford Radcliffe Hospitals NHS Trust** Edward Sharples, Andrea Devaney, Helen Pinnington, Katherine Davies, Sally Ruse, Mel Snelling, Peter Friend; **Royal Berkshire NHS Foundation Trust** Stephen Dawson, Nitin Bhandary, Lindsay Yap, Emma Vaux; **Heart of England NHS Foundation Trust, Birmingham** John Watson, Steve Taylor; **University Hospitals Birmingham NHS Foundation Trust** Paul Cockwell; **University of Liverpool** Saye Khoo; **Royal Liverpool & Broadgreen University Hospitals NHS Trust** Abdul Hammad, Mike Beadsworth ;**Nottingham University Hospitals NHS Trust** Keith Rigg, Catherine Byrne; **Pennine Acute Hospitals NHS Trust, Manchester** Mark Lawton; **Lancashire Care NHS Foundation Trust** John Sweeney**; NHS Greater Glasgow and Clyde** Ellon McGregor, Heather Black, Laura Buist, Ray Fox, Angela Lamb, Kathryn Brown, Ysobel Gourlay, Rak Nandwani, Rebecca Acquah; **University Hospitals of Leicester NHS Trust** Joelle Turner, Maria Martinez, Peter Topham; **West Middlesex** Althea Smith; **Newham University Hospital NHS Trust** Tom Mcmanus. **East Kent Hospitals University NHS Foundation Trust** Michelle Webb **Epsom and St Helier University Hospitals George** Atallah, Steven Estreich. **Mid-Cheshire Hospitals NHS Foundation Trust** Martyn Wood **Gloucestershire Royal Hospital** Alyson Esson, Andrew DeBurgh-Thomas; **Monsall Unit, North Manchester Hospital** Joanne Baxter, Leann Johnson; **Central Manchester University Hospitals** Vincent Lee, Chris Ward, Jennifer Leighton, Marc Vincent**. Spire Manchester Hospital** Benjamin Goorney, Elizabeth Lamerton.

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