Randomized Controlled Trial Comparing Proactive, High-dose Versus Reactive, Low-dose Intravenous Iron Supplementation in Hemodialysis (PIVOTAL): Rationale, Study Design, and Baseline Data

SUPPLEMENTARY APPENDIX

Supplementary Appendix 1. Study sites and principal investigators

England

Basildon & Thurrock Hospital, Basildon: Georgia Winnett; *Bradford Teaching Hospital*, Bradford: Habib Akbani; *Churchill Hospital*, Oxford: Christopher Winearls; *City General Hospital*, Stoke-on-Trent: Julie Wessels; *Coventry University Hospital*, Coventry: Waqar Ayub; *Derriford Hospital*, Plymouth: Andrew Connor; *Freeman Hospital*, Newcastle: Alison Brown; *Gloucestershire Royal Hospital*, Gloucestershire: Jim Moriarty; *Guy's & St Thomas' Hospital*, London: Paramit Chowdury; *Hammersmith Hospital*, London: Megan Griffiths; *Heartlands Hospital*, Birmingham: Indranil Dasgupta; *Hull Royal Infirmary*, Hull: Sunil Bhandari; *Kent & Canterbury Hospital*, Canterbury: Timothy Doulton; *King's College Hospital*, London: Iain Macdougall; *Leicester General Hospital*, Leicester: Jonathan Barratt; *Lister Hospital*, Stevenage: Enric Vilar; *Manchester Royal Infirmary*, Manchester: Sandip Mitra; *New Cross Hospital*, Wolverhampton: Babu Ramakrishna, Johann Nicholas; *Norfolk & Norwich Hospital*, Norwich: Calum Ross; *Northern General Hospital*, Sheffield: Arif Khwaja; *Nottingham City Hospital*, Nottingham: Matt Hall; *Queen Alexandra Hospital*, Portsmouth: Adam Kirk; *Queen Elizabeth Hospital*, Birmingham: Stuart Smith, Mark Jesky, Clara Day; *Royal Berkshire Hospital*, Reading: Bassam Alchi; *Royal Cornwall Hospital*, Cornwall: Jon Stratton; *Royal Devon & Exeter Hospital*, Exeter: Helen Clarke; *Royal Free Hospital*, London: Stephen Walsh; *Royal Liverpool Hospital*, Liverpool: Rebecca Brown; *Royal London Hospital*, London: Kieran McCafferty; *Royal Preston Hospital*, Preston: Laurie Solomon; *Royal Shrewsbury Hospital*, Shrewsbury: Suresh Ramadoss, Babu Ramakrishna; *Royal Sussex Hospital*, Brighton: Kolitha Basanyake, Sarah Lawman; *Salford Royal Hospital*, Manchester: Philip Kalra; *Southend University Hospital*, Southend: Gowrie Balasubramaniam; *Southmead Hospital*, Bristol: Albert Power; *St George's Hospital*, London: Debasish Banerjee; *St Helier Hospital*, Carlshalton: Pauline Swift; *St James' Hospital*, Leeds: Matt Wellberry-Smith; *University Hospital*, Aintree: Christopher Goldsmith; *Wirral University Teaching Hospital*, Wirral: Thomas Ledson

Wales

Morriston Hospital, Swansea: Ashraf Mikhail; *University Hospital*, Cardiff: Ruth Benzimra

Scotland

Ninewells Hospital, Dundee: Samira Bell, Alison Severn; *Royal Infirmary of Edinburgh*, Edinburgh: John Neary; *Victoria Hospital*, Kirkcaldy: Arthur Doyle; *Queen Elizabeth University Hospital*, Glasgow: Peter Thomson

N. Ireland

Altnagelvin Hospital, Derry: Girish Shivashankar; *Antrim Area Hospital*, Antrim: Stephanie Bolton, Michael Quinn; *Belfast City Hospital*, Belfast: Peter Maxwell; *Daisy Hill Hospital*, Newry: John Harty

Steering Committee

Iain Macdougall (chair), Ian Ford (biostatistician), Sunil Bhandari, Philip Kalra, Christopher Winearls, Stefan Anker, Ken Farrington, John McMurray, Charlie Tomson, David Wheeler

Endpoint Adjudication Committee

John McMurray (chair), Patrick Mark, Eugene Connolly, Pardeep Jhund, Michael MacDonald, Mark Petrie, Matthew Walters

Independent Data Monitoring Committee

Alan Jardine (chair), Janet Peacock (biostatistician), Chris Isles, Donal Reddan

Supplementary Appendix 2. Substantial amendments to study protocol

<table>
<tr><th>Version</th><th>Date</th><th>Original text</th><th>Amended text</th><th>Rationale</th></tr>
<tr><td>1.0</td><td>28 June 2013</td><td>Version approved by ethics committee and the Medicines and Healthcare products Regulatory Agency (MHRA) prior to recruitment beginning</td><td></td><td></td></tr>
<tr><td>2.0</td><td>18 December 2013</td><td>Dosing of IV iron in the low-dose, reactive arm:
If ferritin <100 µg/L, subjects will receive IV iron sucrose 200 mg undissolved as a slow bolus injection during the first dialysis session of the week following the monthly blood tests (usually the second week of the calendar month), regardless of TSAT.

If ferritin >100 µg/l and TSAT <20%, then patient will receive IV iron sucrose 100 mg as a slow bolus intravenous injection during the first dialysis session of the week following the monthly blood tests (usually the second week of the calendar month).

If ferritin >200 µg/l and TSAT >20%, then the dose of iron will be withheld.</td><td>Patients will receive IV iron sucrose, undiluted, as a slow bolus injection during the first dialysis session of the week following the monthly blood tests (usually the second week of the calendar month).
The monthly dose to be administered is as follows;

<table><tr><td>If ferritin <100 mcg/L and TSAT <40%</td><td>IV iron sucrose 200 mg</td></tr><tr><td>If ferritin 100-200 mcg/L and TSAT <40%</td><td>IV iron sucrose 200 mg</td></tr><tr><td>If ferritin >200 mcg/L and TSAT ≤20%</td><td>IV iron sucrose 100 mg</td></tr><tr><td>If ferritin >200 mcg/L and TSAT >20%</td><td>Withhold dose</td></tr><tr><td>If TSAT ≥40% (regardless of ferritin level)</td><td>Withhold dose</td></tr></table></td><td>Amended to provide more clarity on dose to be administered.</td></tr>
<tr><td>3.0</td><td>11 July 2014</td><td>Inclusion criteria:
All participants will be identified from dialysis units around the UK, and any patient who is new to dialysis or has dialysed for less than 12 months will be eligible provided they satisfy the inclusion and exclusion criteria.</td><td>Inclusion criteria:
All participants will be identified from dialysis units around the UK, and any patient who is new to haemodialysis or has dialysed for less than 12 months will be eligible provided they satisfy the inclusion and exclusion criteria. Eligible patients must provide consent before the 0-12 month dialysis period is exceeded. Patients who have received previous haemodialysis, peritoneal dialysis or renal transplant(s) may enter the study. Home haemodialysis patients may not enter the study.</td><td>Change in protocol to allow patients to be consented up to 12 months on haemodialysis.

To provide clarity that previous patients who have had HD, PD or renal transplants may be include.

To provide clarity that home haemodialysis patients may not be included.</td></tr>
<tr><td>3.0</td><td>11 July 2014</td><td></td><td>Informed consent:
Written Informed Consent must be sought from eligible patients who have been on haemodialysis for 0-12 months. Patients who provide consent must be randomised before their length of time on haemodialysis exceeds 18 months.</td><td>Protocol change to allow patients to be consented between 0-12 months on haemodialysis, and to allow a further 6 months to randomise the patient.</td></tr>
<tr><td>4.0</td><td>11 May 2015</td><td>Dosing:
Patients will receive IV iron sucrose, undiluted, as a slow</td><td>Dosing:
Patients will receive IV iron sucrose, undiluted, as a slow</td><td>To allow sites to administer IV iron by intravenous infusion if this is the sites</td></tr>
</table>

<table>
<tr><th>Version</th><th>Date</th><th>Original text</th><th>Amended text</th><th>Rationale</th></tr>
<tr><td></td><td></td><td>bolus injection….</td><td>bolus injection (or by intravenous infusion)….</td><td>standard practice.</td></tr>
<tr><td>5.0</td><td>12 January 2016</td><td>Dosing regimen (reactive IV iron arm):

Patients will receive IV iron sucrose, undiluted, as a slow bolus injection (or by intravenous infusion) during the first dialysis session of the week following the monthly blood tests (usually the second week of the calendar month).

<table><tr><td>If ferritin <100 mcg/L and TSAT <40%</td><td>IV iron sucrose 200 mg</td></tr><tr><td>If ferritin 100-200 mcg/L and TSAT <40%</td><td>IV iron sucrose 200 mg</td></tr><tr><td>If ferritin >200 mcg/L and TSAT ≤20%</td><td>IV iron sucrose 100 mg</td></tr><tr><td>If ferritin >200 mcg/L and TSAT >20%</td><td>Withhold dose</td></tr><tr><td>If TSAT ≥40% (regardless of ferritin level)</td><td>Withhold dose</td></tr></table></td><td>Dosing regimen (reactive IV iron arm):

Patients will receive IV iron sucrose, undiluted, as a slow bolus injection (or by intravenous infusion) during the first one or two (see table below) dialysis sessions of the week following the monthly blood tests (usually the second week of the calendar month).

<table><tr><td>If ferritin <100 mcg/L and TSAT <40%</td><td>IV iron sucrose 200 mg during each of the first two dialysis sessions of the week</td></tr><tr><td>If ferritin 100-200 mcg/L and TSAT <40%</td><td>IV iron sucrose 200 mg during each of the first two dialysis sessions of the week</td></tr><tr><td>If ferritin >200 mcg/L and TSAT ≤20%</td><td>IV iron sucrose 100 mg during the first dialysis session of the week</td></tr><tr><td>If ferritin >200 mcg/L and TSAT >20%</td><td>Withhold dose</td></tr><tr><td>If TSAT ≥40% (regardless of ferritin level)</td><td>Withhold dose</td></tr></table></td><td>Change to allow patients in Arm 2 (reactive IV iron) to receive slightly more iron than is allowed in previous protocol. This has been instigated by the recognition that several patients in the reactive arm of the study were becoming iron deficient and have not been able to maintain ferritin levels of more than 100 mcg/L.</td></tr>
<tr><td>6.0</td><td>23 December 2016</td><td>Dosing regimen (reactive IV iron arm):

<table><tr><td>If ferritin <100 mcg/L and TSAT <40%</td><td>IV iron sucrose 200 mg during each of the first two dialysis sessions of the week</td></tr><tr><td>If ferritin 100-200 mcg/L and TSAT <40%</td><td>IV iron sucrose 200 mg during each of the first two dialysis sessions of the week</td></tr><tr><td>If ferritin >200 mcg/L and TSAT ≤20%</td><td>IV iron sucrose 100 mg during the first dialysis session of the week</td></tr><tr><td>If ferritin >200 mcg/L and TSAT >20%</td><td>Withhold dose</td></tr><tr><td>If TSAT ≥40% (regardless of ferritin</td><td>Withhold dose</td></tr></table></td><td>Dosing regimen (reactive IV iron arm):

<table><tr><td>If ferritin <100 mcg/L and TSAT <40%</td><td>IV iron sucrose 200 mg during each of the first two dialysis sessions of the week</td></tr><tr><td>If ferritin 100-200 mcg/L and TSAT <40%</td><td>IV iron sucrose 200 mg during each of the first two dialysis sessions of the week</td></tr><tr><td>If ferritin 201-700 mcg/L and TSAT ≤20%</td><td>IV iron sucrose 100 mg during the first dialysis session of the week</td></tr><tr><td>If ferritin >200 mcg/L and TSAT >20%</td><td>Withhold dose</td></tr><tr><td>If ferririn >700 mcg/L and/or TSAT ≥40%</td><td>Withhold dose</td></tr></table></td><td>To clarify that there is a safety cut off for ferritin >700mcg/L for arm 2 patients.</td></tr>
</table>

Version	Date	Original text	Amended text	Rationale
		level)		
7.0	4 February 2018	For the non-inferiority analysis, the per protocol population (PPP) will be defined as the population of subjects that have a valid randomisation and receive at least one dose of study drug and no major protocol deviation.	For the non-inferiority analysis, the per protocol population (PPP) will be defined as the population of subjects that have a valid randomisation and receive at least one dose of study drug and no major protocol deviations in relation to the inclusion/exclusion criteria. Transplant patients will be censored at the date of transplant and any events prior to transplant will be included in the analysis; any events subsequent to the transplant will not be included in the analysis.	To clarify that the PPP will be defined as those patients in whom there have been no protocol deviations specifically in relation to the inclusion/exclusion criteria. To clarify that for the analysis, transplant patients will be censored at the date of transplant.
8.0	16 April 2018	Endpoints: PRIMARY ENDPOINTS Time to all-cause death or a composite of myocardial infarction, stroke, and hospitalisation for heart failure. SECONDARY EFFICACY • Incidence of all-cause death and a composite of myocardial infarction, stroke, and hospitalisation for heart failure as recurrent events. • Time to (and incidence of) all-cause death • Time to (and incidence of) composite cardiovascular event • Time to (and incidence of) myocardial infarction • Time to (and incidence of) stroke • Time to (and incidence of) hospitalisation for heart failure • ESA dose requirements • Transfusion requirements • EQ-5D QOL and KDQOL SECONDARY SAFETY • Vascular access thrombosis • All-cause hospitalisation • Hospitalisation for infection • Infection episodes	Endpoints: PRIMARY ENDPOINTS Time to first event: all-cause death or a composite of myocardial infarction, stroke, and hospitalisation for heart failure. SECONDARY EFFICACY • Incidence of all-cause death and a composite of myocardial infarction, stroke, and hospitalisation for heart failure as recurrent events. • Time to (and incidence of) all-cause death • Time to (and incidence of) first composite cardiovascular event • Time to (and incidence of) first myocardial infarction • Time to (and incidence of) first stroke • Time to (and incidence of) first hospitalisation for heart failure • ESA dose requirements • Transfusion requirements • EQ-5D QOL and KDQOL SECONDARY SAFETY • Time to first vascular access thrombosis • Time to first all-cause hospitalisation • Time to first hospitalisation for infection • Number of infection episodes	To clarify that the primary endpoint is **time to first event** for all-cause death or a composite of myocardial infarction, stroke, and hospitalisation for heart failure. To clarify that the secondary efficacy is • Time to (and incidence of) **first** composite cardiovascular event • Time to (and incidence of) **first** myocardial infarction • Time to (and incidence of) **first** stroke • Time to (and incidence of) **first** hospitalisation for heart failure To clarify that secondary safety is; • **Time to first** vascular access thrombosis • **Time to first** all-cause hospitalisation • **Time to first** hospitalisation for infection • **Number** of infection episodes

Version	Date	Original text	Amended text	Rationale
8.0	16 April 2018	Sample size: Based on previous trials and registries (e.g. the AURORA trial and the UK Renal Registry), it is expected that the primary outcome will be dominated by deaths. In AURORA, the 3-year (the expected average follow-up in our trial) mortality was approximately 40%. The inclusion of non-fatal myocardial infarction, stroke and admission for heart failure is likely to increase this to 50%. Assuming this event rate in the control group, to reject a non-inferiority limit of HR=1.2 with 80% power, 945 participants per group (944 events in total) are required. Adjusting for loss to follow-up due to withdrawal of consent and renal transplantation requires an uplift in the numbers to be recruited of approximately 10%, and gives a total required sample size of 2080.	Sample size: Based on previous trials and registries (e.g. the AURORA trial and the UK Renal Registry), it is expected that the primary outcome will be dominated by deaths. In AURORA, the 3-year (the expected average follow-up in our trial) mortality was approximately 40%. The inclusion of non-fatal myocardial infarction, stroke and admission for heart failure is likely to increase this to 50%. The initial sample size calculations assumed this event rate in the control group. To reject a non-inferiority limit of HR=1.20 with 80% power, 945 participants per group (944 first primary events in total) are required. Adjusting for loss to follow-up due to withdrawal of consent and renal transplantation requires an uplift in the numbers to be recruited of approximately 10%, and gives a total required sample size of 2080. On review of blinded endpoint accrual, it became clear that it would not be possible to achieve 944 first primary endpoints. Hence, the target number of first primary endpoints has been revised to a minimum of 631, which will give a minimum of 80% power to reject a non-inferiority limit of HR = 1.25.	At the time the power calculation for PIVOTAL was performed, a hazard ratio of 1.2 was deemed appropriate. The hazard ratio for non-inferiority for many randomised controlled trials approved by the FDA has, in recent years, relaxed somewhat from 1.2 to 1.3. The steering committee have recommended that the study be re-powered with a hazard ratio of 1.25 and this requires a minimum of 631 first primary endpoints.

Supplementary Table 1. Baseline characteristics of PIVOTAL trial cohort and adult HD patients in the UK Renal Registry

Characteristic	PIVOTAL Trial (N=2141)	UK Renal Registry Adult HD Patients[a] (N=24,828)
Age (years)	65 (52, 75)	67.2 (54.6, 77.0)
Gender, %		
Male	65.3	61.5
Female	34.7	38.5
Ethnicity, %		
White	79	72
Black	9	11
Asian	9	14
Other	3	3
Diabetes, %	44	44
Smoking status, %		
Current	12	13[b]
Former	25	
Never	63	87[b]
Weight (kg)	80 (67, 95)	75 (63, 89)
BMI (kg/m^2)	28 (24, 33)	27 (23, 31)
Systolic BP (mmHg)[c]	144 (128, 160)	142 (126, 159)
Diastolic BP (mmHg)[c]	73 (64, 83)	71 (62, 82)
Hemoglobin (g/dL)	10.6 (9.6, 11.5)	11.0 (10.0, 11.8)
Ferritin (μg/L)	216 (133, 304)	402 (244, 621)
ESA dose (IU/week)[d]	8000 (5000, 12,000)	7750 (4500, 12,000)
Primary cause of renal failure, %		
Diabetic nephropathy	33.4	24.3
Glomerular disease	18.6	14.6
Hypertension	11.0	7.2
Tubulointerstitial disease	9.4[e]	N/A
Renovascular disease	6.9	5.1
Polycystic kidney disease	5.5	5.7
Other	6.1	23.2[f]
Unknown/Uncertain	9.2	15.6

Continuous variables are shown as median (LQ, UQ). Variables listed on table 3 and not included above were not available from the UK Renal Registry dataset.
[a]Unpublished data provided by R Steenkamp and the UK Renal Registry and represent data as of Q4 2016.
[b]Coded as "yes" or "no" in the UK Renal Registry.
[c]BP measurements represent pre-HD assessments.
[d]ESA dose for darbepoetin and methoxypolyethylene glycol epoetin beta converted to IU/week using standard conversion factors.
[e]Includes pyelonephritis, reflux nephropathy, and obstructive uropathy.
[f]Includes "other primary renal diagnosis" and pyelonephritis.