Supplementary information for:

Estimating the comparative effectiveness of dynamic treatment strategies for medication use and dosage: application of marginal structural models to emulate a hypothetical target trial using observational data

Further information on the data extraction

Data were extracted from 2004 to 2016. Centres reporting fewer than 60% of haemodialysis patients being treated with ESAs in a quarter year were considered to have incomplete data and their data for that quarter were excluded. We restricted analyses to patients who were prescribed darbepoetin, because although approximately equivalent doses of other drugs such as epoetin can be defined, the distribution of doses was not sufficiently similar to permit combined analyses. Standard UKRR data provided information on age, sex, year of starting renal replacement therapy, primary renal disease (diabetes, glomerulonephritis, hypertension, polycystic kidneys, pyelonephritis, renal vascular disease, other or uncertain), co-morbidities (angina, angioplasty, claudication, chronic obstructive pulmonary disease, diabetes not causing ESRF, ischaemic / neuropathic ulcers, liver disease, malignancy, previous myocardial infarction within last 3 months prior to starting RRT, previous myocardial infarction > 3 months ago, previous CAGB or coronary angioplasty, amputation for peripheral vascular disease, symptomatic cerebrovascular disease, heart failure, and whether the patient is a smoker) and date of death, which was independently ascertained from a death registry through routine tracing conducted by the UKRR against the NHS Spine.

Covariates

These were: cubic splines for Hb (g/L) and lagged Hb from previous month, white blood cell count (<6, 6-6.9, 7-7.9, 8-8.9, 9+ 10^9/L), albumin (<35, 35-39, 40+ g/L or missing), ferritin (<300, 300-449, 500+ µg/L or missing), calcium (adjusted for albumin; <2.3, 2.3-2.39, 2.4-2.49, 2.5+ mg/dL or missing), C-reactive protein (0 or not tested, 0.1 to 4.9, 5 to 19.9, 20+ mg/L), urea reduction ratio (dialysis adequacy; <60, 60 to 69, 70 to 74, 75-79, 80+ %) number of blood tests in the previous 28 days (0, 1,

2, 3, 4+), cubic splines for months since joining the study. We also included non-time-varying covariates: age at start of follow up, gender, primary renal disease (diabetes, glomerulonephritis, polycystic, pyelonephritis or other), co-morbidities present at the start of RRT (angina, angioplasty, claudication, chronic obstructive pulmonary disease, diabetes not causing ESRF, ischaemic / neuropathic ulcers, liver disease, malignancy, previous myocardial infarction within last 3 months prior to starting RRT, previous myocardial infarction >3 months prior to start of RRT, previous CAGB or coronary angioplasty, amputation for peripheral vascular disease, symptomatic cerebrovascular disease, heart failure, and whether the patient was a smoker) and renal centre.

Further details on how data were organised in discrete time periods

For the first 3 months of the study, lagged values of treatment from 2 and 3 months previously are defined to be equal to the baseline value of that variable. The darbepoetin dose recorded in each month was the new dose if there was a dose change in that month, or that from the previous month if there was no dose change. Darbepoetin doses were only carried forward while the prescription was still valid (i.e. prior to the end date of the prescription). The Hb recorded in each month was the latest measurement that occurred before a dose change, or if there was no dose change, we used the last measurement of the previous month. If there were no changes to darbepoetin dose and no change in Hb for 6 months, the patient was assumed to be lost to follow-up.

Withdrawal from the target trial

Other than because of non-adherence to the assigned treatment strategy or the occurrence of the outcome event, patients were censored if they (1) changed from haemodialysis to peritoneal dialysis, (2) had a kidney transplant or (3) were lost to follow-up. Loss to follow-up occurred if we stopped getting Hb and ESA dose information, but had no other information on the patient, such as, if they

changed from haemodialysis to peritoneal dialysis, had a kidney transplant, or died. Some patients who transferred out of a centre submitting data were lost to follow-up. We created indicator variables for each censoring variable, which took the value of 0 if the patient remained uncensored at month *t*, and 1 otherwise. $\overline{C_k}(t)$ denotes censoring history (i.e. the vector of censoring indicator values from baseline to month *t*) for withdrawal reason *k*. Separate logistic models were used to calculate the probability of remaining uncensored up to month *t*, for each censoring variable. To derive each patient's estimated probability of their complete censoring history up to each month, we multiplied the estimated probabilities of being uncensored for each month cumulatively over time:

$$W^*(t) = \prod_0^t \frac{1}{Pr(C_k(t) = 0 | \overline{C_k}(t-1) = 0, \bar{L}(t), \bar{A}(t-1), T > t}$$

for individuals not censored up to the current month.

eTable 1 Specification and emulation of the target trial

Component	Target trial	Emulation
Design	Multicentre open-label two-parallel arm superiority randomised trial.	
Aim	To compare a lower with a higher Hb target, implemented using a specified dosing strategy.	Same
Study population	Adult haemodialysis patients in UK renal centres between 2004 and 2016.	Same
Eligibility criteria	People aged ≥18 years on haemodialysis for at least three months and on darbepoetin, or, not on darbepoetin with a Hb<110 g/L.	Same
Exclusions	People who, at the start of their eligibility, have a high darbepoetin dose (≥120 darbepoetin mcg/week) and low Hb (<80 g/L).	Same
Follow-up	Start: after completing three months of haemodialysis at a contributing renal centre. End: eight months after baseline, death, or loss to follow-up, whichever happens first.	Same
Intervention strategies	Lower (target range 95-115 g/L) versus higher (target range 105-125 g/L) Hb strategies. Both strategies follow the dose change decisions protocol (Figure 2) and acceptable dose changes table (Table A2).	Same
Allowances	Patients allowed to come off darbepoetin for a period if their Hb is greater than the upper target.	A grace period of one month* with patients allowed to come off darbepoetin for a period if their Hb is greater than the upper target.
Treatment assignment	Patients are randomly assigned to one or the other strategy	Data for each patient is copied ("cloned"), and one copy is assigned to each treatment strategy at baseline.
Outcome	All-cause mortality.	Same
Withdrawal	(1) Change to peritoneal dialysis, (2) receipt of a kidney transplant or (3) loss to follow-up.	Same
Causal contrast	Per protocol.	Same
Statistical analysis	Patients are censored when they deviate from their assigned strategy. IP weights for artificial censoring are estimated as a function of treatment and covariate history.	Same

* We allowed a grace period of up to one month for dose changes to be implemented after the dosing rules stated that the dose should have been changed

eTable 2 Acceptable dose changes (mcg/week)

From:	To: 0	0.1-2.5	2.51-5	5.1-10	10.1-15	15.1-20	20.1-25	25.1-30	30.1-40	40.1-50	50.1-60	60.1-70	70.1-80	80.1-100	100.1-120	120.1 - 150
0	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†	×†	×†	×†	×†	×†
0.1-2.5	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†	×†	×†	×†	×†	×†
2.51-5	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†	×†	×†	×†	×†	×†
5.1-10	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†	×†	×†	×†	×†	×†
10.1-15	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†	×†	×†	×†	×†	×†
15.1-20	✓	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†	×†	×†	×†	×†
20.1-25	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†	×†	×†	×†
25.1-30	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†	×†	×†
30.1-40	×*	×*	×*	×*	×*	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†
40.1-50	×*	×*	×*	×*	×*	×*	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†
50.1-60	×*	×*	×*	×*	×*	×*	×*	✓	✓	✓	✓	✓	✓	✓	✓	×†
60.1-70	×*	×*	×*	×*	×*	×*	×*	×*	✓	✓	✓	✓	✓	✓	✓	✓
70.1-80	×*	×*	×*	×*	×*	×*	×*	×*	✓	✓	✓	✓	✓	✓	✓	✓
80.1-100	×*	×*	×*	×*	×*	×*	×*	×*	×*	✓	✓	✓	✓	✓	✓	✓
100.1-120	×*	×*	×*	×*	×*	×*	×*	×*	×*	×*	✓	✓	✓	✓	✓	✓
120.1-150	×*	×*	×*	×*	×*	×*	×*	×*	×*	×*	×*	✓	✓	✓	✓	✓

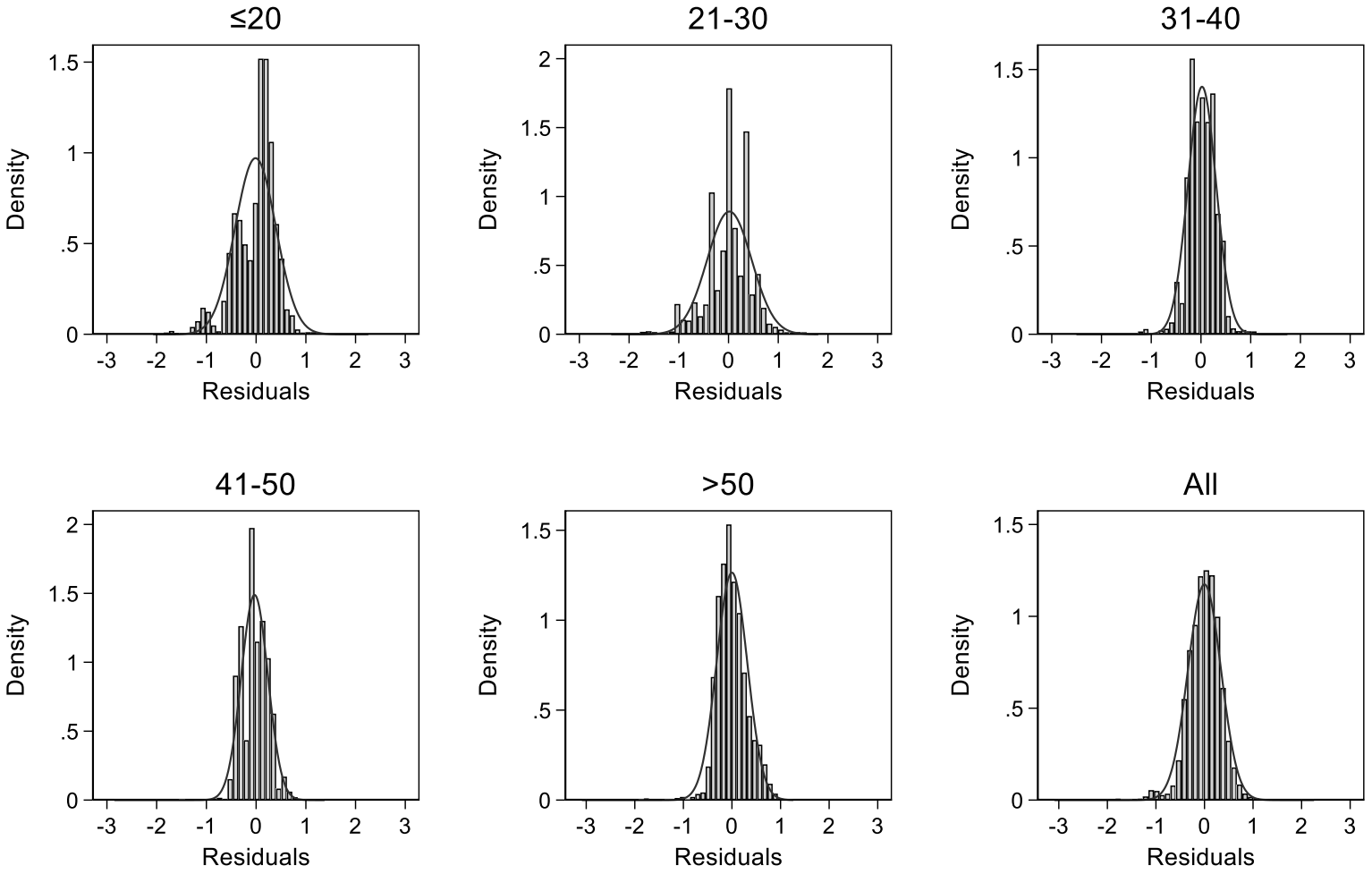
Doses are presented as the weekly darbepoetin dose.

✓ Dose changes are acceptable

×* Dose changes are not acceptable unless the Hb is above the upper target

×† Dose changes are not acceptable unless a person previously had a ×* dose change, and their Hb is now in target range or below the lower target. Patient allowed to go up to their previous ×* dose, but not higher

eFigure 1 Histograms of residuals by categories of predicted values on darbepoetin dose scale from linear regression model for log darbepoetin dose



eTable 3 Classification of categories for multinomial regression

Observed dose change	What the dosing protocol said for the low Hb strategy	What the dosing protocol said for the high Hb strategy	Coding
Moved to zero dose	N/A	N/A	1
Decreased dose	Decrease dose	Decrease dose	4
	Decrease dose	No change in dose	X
	Decrease dose	Within threshold, acceptable changes allowed	4
	Decrease dose	Increase dose	X
	No change in dose	Decrease dose	X
	No change in dose	No change in dose	2
	No change in dose	Within threshold, acceptable changes allowed	X*
	No change in dose	Increase dose	X
	Within threshold, acceptable changes allowed	Decrease dose	X
	Within threshold, acceptable changes allowed	No change in dose	3
	Within threshold, acceptable changes allowed	Within threshold, acceptable changes allowed	4
	Within threshold, acceptable changes allowed	Increase dose	3
	Increase dose	Decrease dose	X
	Increase dose	No change in dose	X
	Increase dose	Within threshold, acceptable changes allowed	X
	Increase dose	Increase dose	2
No changed in dose	N/A	N/A	5
Increased dose	Decrease dose	Decrease dose	8
	Decrease dose	No change in dose	X
	Decrease dose	Within threshold, acceptable changes allowed	7
	Decrease dose	Increase dose	X
	No change in dose	Decrease dose	X
	No change in dose	No change in dose	8
	No change in dose	Within threshold, acceptable changes allowed	7
	No change in dose	Increase dose	X
	Within threshold, acceptable changes allowed	Decrease dose	X
	Within threshold, acceptable changes allowed	No change in dose	X*
	Within threshold, acceptable changes allowed	Within threshold, acceptable changes allowed	6
	Within threshold, acceptable changes allowed	Increase dose	6
	Increase dose	Decrease dose	X
	Increase dose	No change in dose	X
	Increase dose	Within threshold, acceptable changes allowed	X
	Increase dose	Increase dose	6

Category codes: (1) go off darbepoetin (i.e. move to zero dose) (2) unacceptable decrease in dose for both strategies (3) acceptable decrease for low Hb strategy only (4) acceptable decrease both strategies (5) stay the same (6) acceptable increase for both strategies (7) acceptable increase for high Hb strategy only (8) unacceptable increase for both strategies

N/A Not applicable as coding did not depend on what the protocol said for these categories

X Not possible with Hb targets/protocol

X* Theoretically possible, but not observed in data when previous dose was 2.5, 5, 120 or 150 mcg/week

eTable 4 Acceptable dose changes for the dosing ladder (mcg/week)

From:	To: 0	2.5	5	10	15	20	25	30	40	50	60	70	80	100	120	150
0	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†	×†	×†	×†	×†	×†
2.5	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†	×†	×†	×†	×†	×†
5	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†	×†	×†	×†	×†	×†
10	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†	×†	×†	×†	×†	×†
15	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†	×†	×†	×†	×†	×†
20	✓	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†	×†	×†	×†	×†
25	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†	×†	×†	×†
30	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†	×†	×†
40	×*	×*	×*	×*	×*	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†	×†
50	×*	×*	×*	×*	×*	×*	✓	✓	✓	✓	✓	✓	✓	✓	×†	×†
60	×*	×*	×*	×*	×*	×*	×*	✓	✓	✓	✓	✓	✓	✓	✓	×†
70	×*	×*	×*	×*	×*	×*	×*	×*	✓	✓	✓	✓	✓	✓	✓	✓
80	×*	×*	×*	×*	×*	×*	×*	×*	✓	✓	✓	✓	✓	✓	✓	✓
100	×*	×*	×*	×*	×*	×*	×*	×*	×*	✓	✓	✓	✓	✓	✓	✓
120	×*	×*	×*	×*	×*	×*	×*	×*	×*	×*	✓	✓	✓	✓	✓	✓
150	×*	×*	×*	×*	×*	×*	×*	×*	×*	×*	×*	✓	✓	✓	✓	✓

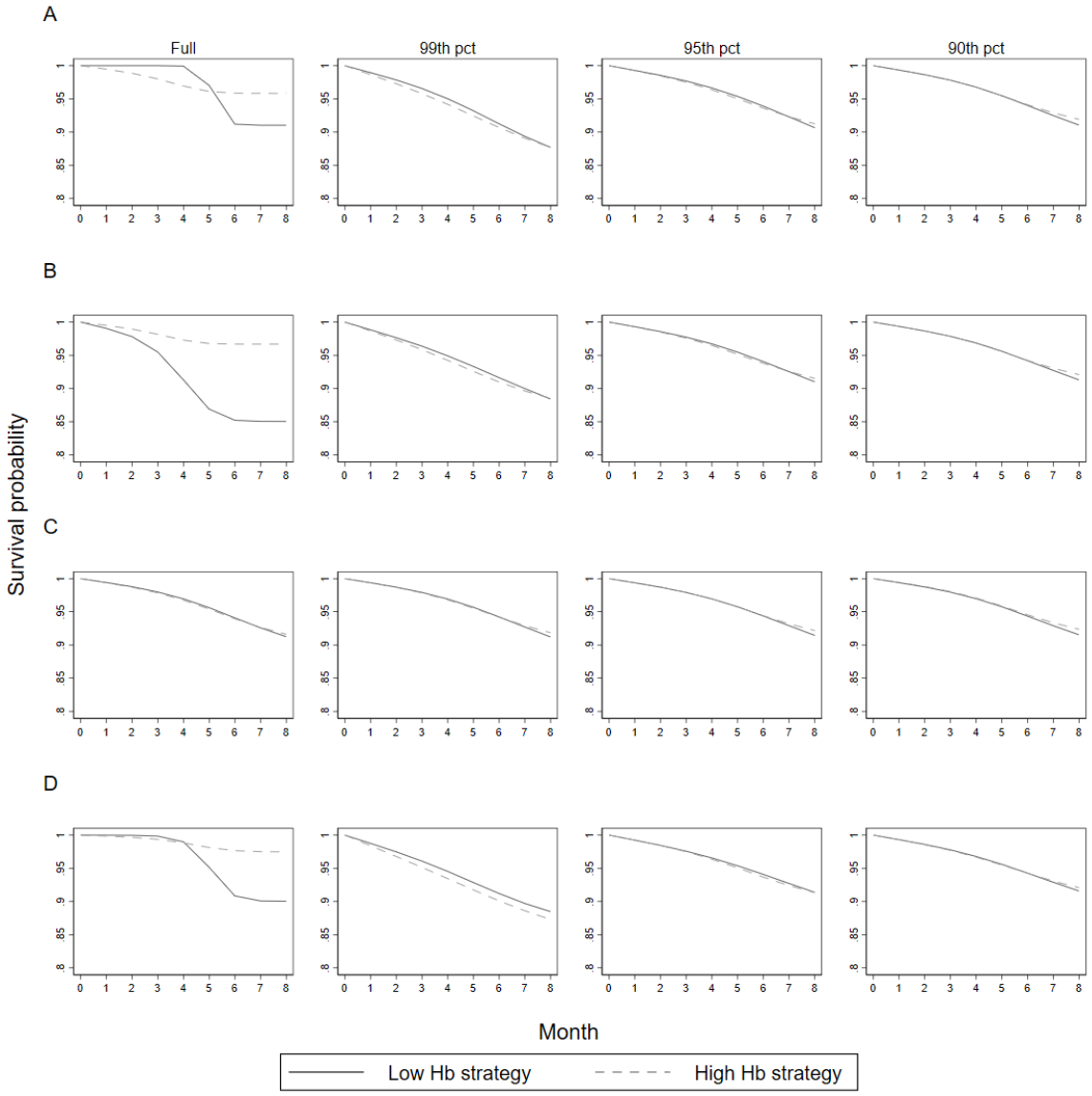
Doses are presented as the weekly darbepoetin dose.

✓ Dose changes are acceptable

×* Dose changes are not acceptable unless the Hb is above the upper target

×† Dose changes are not acceptable unless a person previously had a ×* dose change, and their Hb is now in target range or below the lower target. Patient allowed to go up to their previous ×* dose, but not higher

eFigure 2 Estimated weighted survival curves for all-cause mortality comparing high versus low haemoglobin strategies, by method A-D and different weight truncations.



Notes: Full means that no truncation has taken place on the weights. 99th pct means the weights have been truncated at the 99th percentile etc. Method A: Logistic regression models for zero dose and **normal linear regression** for log dose. Method B: Logistic regression models for zero dose and **heteroscedastic linear regression** for log dose. Method C: Logistic regression models for zero dose, **heteroscedastic linear regression** for log dose and **multinomial regression** for coming from very low and very high doses. Method D: **Ordinal regression** model for all levels of dose.

eFigure 3 Estimated survival curves for all-cause mortality comparing high versus low haemoglobin strategies, for the unweighted analysis.