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Evaluation of a national digital pre-implantation biopsy service for deceased-donor kidney transplantation in the UK (Pithia trial): a stepped-wedge cluster randomised registry trial

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Summary

Background Pre-implantation biopsy may help select kidneys retrieved from elderly deceased donors for transplantation, but concerns persist that it may cause unnecessary discard of kidneys that would have provided acceptable transplant function. The PITHIA trial tested the hypothesis that introduction of a National Digital Pathology Service (NDPS) would increase the proportion of kidneys transplanted from elderly donors and/or improve their function.

Methods A stepped-wedge cluster randomised controlled registry trial delivered the NDPS to 22 UK kidney transplant centres (clusters) in 5 sequences at four-monthly intervals, using a restricted randomisation technique to ensure similar cluster sizes in the intervention and control status. Upon access to the intervention, centres could request urgent pre-implantation biopsy on kidneys from deceased donors aged 60 years or older. Co-primary outcome measures were the proportion of kidneys transplanted upon first offer according to whether the centre had access or not to the biopsy service, and the 1-year eGFR of the kidneys that were transplanted. Analysis adjusts for clustering and underlying secular trends, with 97.5% Confidence Intervals (CI) reported to reflect the two co-primary outcomes. The trial is complete (Trial Registration Number: ISRCTN 11708741).

Findings The trial commenced on 1st October 2018 and ended on 31st January 2022. Of the 2502 eligible kidneys offered, 1355 single and 67 dual transplants were performed. Regarding the first primary endpoint, a non-significantly lower proportion of those kidneys first offered to centres with access to the biopsy service were transplanted compared with those offered to centres without access (295 of 1241 (23.8%) vs. 377 of 1261 (29.9%): adjusted Odds Ratio (97.5% CI) 0.91 (0.60–1.39); p = 0.6083). For the second primary endpoint, the adjusted mean (SE) 1-year eGFR of the transplant kidneys was similar, irrespective of whether the implanting centre had access to the biopsy service or not (43.7 (1.3) ml/min/1.73 m^2 vs. 42.2 (1.3) ml/min/1.73 m^2; adjusted mean difference (97.5% CI) 1.53 (–2.33 to 5.40); p = 0.37). Secondary outcome analysis of how the biopsy service was adopted revealed that biopsies were performed on 287 of the 1493 (19.2%) kidneys offered to at least one centre with access to the biopsy service, with marked variation between transplant centres in requests for biopsy, and in implantation rates of biopsied kidneys. Nevertheless, 191 (66.6%) of biopsied kidneys were transplanted, compared with 643 of the 1009 (63.7%) kidneys only ever offered to centres without biopsy access, and 588 of the 1206 (48.8%) kidneys that were not biopsied, despite being offered to at least one centre with biopsy access.

Interpretation Implementation of the NDPS did not significantly increase transplantation rates of elderly deceased donor kidneys upon first offer, nor improve 1-year eGFR of the transplanted kidneys. This may reflect inter-centre variation in adoption and application of the biopsy service; such variations would need to be considered when designing future studies of pre-implantation biopsy analysis.

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Keywords: Pre-implantation biopsy analysis; Deceased donor kidney transplantation; Stepped wedge cluster randomised trial; National digital pathology service

Introduction

There are over 30,000 people in the UK with end-stage kidney disease (ESKD) who are currently on, or approaching dialysis, and for many, transplantation is a better option, offering a survival advantage[1] and improved quality of life.[2] It is also substantially cheaper.[3] The demand this creates results in typical waiting times for a deceased donor kidney transplant of around 2–3 years[4] (often longer in other countries[5]), and with the predicted threefold increase in the incidence of ESKD over the next decade,[3,6] waiting times for transplantation are likely to rise considerably unless transplant numbers increase simultaneously.

Increased use of elderly donors has the most immediate potential for expanding the deceased donor pool. Approximately 40% of kidneys offered from donors over 60 years old are currently not transplanted, reflecting concerns over poor transplant outcomes[7] that relate to loss of nephron mass and decline in eGFR as one ages. In recognition that this decline is variable

Research in context

Evidence before this study

Compared to other forms of renal replacement therapy, kidney transplantation offers survival, quality of life, and health economic advantages. Shortage of organs means, however, that individuals typically wait several years for a transplant. Because of concerns relating to poor transplant outcomes, the pool of elderly deceased donors remains underutilised, and transplantation of those kidneys from donors aged 60 years or older that are currently declined or discarded would potentially increase deceased donor kidney transplant numbers by about a quarter, thereby shortening transplant waiting times considerably.

Although pre-implantation biopsy analysis is widely, but variably, used to help determine the suitability of elderly deceased donor kidneys for transplantation, a search (1st April 2025) of Medline and Pubmed for the terms, 'kidney' AND either 'pre-implantation biopsy' or 'implantation biopsy', coupled with citation cross-checking on SCOPUS, confirms that only one prospective evaluation of its impact has been reported. This study concluded that pre-implantation biopsy of elderly deceased donor kidneys resulted in improved kidney transplant outcomes. Since that landmark study, several retrospective single-centre and registry analyses have been performed. These have reached contradictory conclusions about the correlation between implant biopsy findings and longer-term transplant outcome, with several raising concerns that biopsy may result in unnecessary discard of kidneys that would otherwise have provided acceptable transplant function. Hence, pre-implantation biopsy analysis remains one of the most contested topics in clinical transplantation.

Added value of this study

This study represents the first prospective randomised trial evaluation of introduction of a national digital pathology service that provided urgent pre-implantation biopsy analysis to all UK kidney transplant centres. The study was powered to address two primary end-points: proportion of offered kidneys from deceased donors aged 60 or older that were transplanted upon first offer and the 1-year eGFR of the transplanted kidneys. Our analysis demonstrates that provision of a biopsy service did not significantly alter the proportion of offered kidneys transplanted upon first offer, nor the one-year function of those kidneys transplanted.

Implications of all the available evidence

Our randomised trial provides for the first time a prospective evaluation of how preimplantation biopsy availability influences kidney transplant numbers and function. Despite prior publications reporting a correlation between preimplantation biopsy analysis and transplant outcomes, our analysis suggests that introduction of a permanent funded biopsy service may not impact positively upon kidney transplant practice.

(with many kidneys from older donors providing excellent function in the recipient) and manifests as detectable, and quantifiable, chronic injury on standard kidney biopsy, the Italian 'Double Kidney Transplant Group' first proposed the use of pre-implantation biopsy to guide implantation decisions: discard when biopsy revealed severe chronic damage, transplant as two separate kidney transplants for no or minimal damage; and implantation of both kidneys as a 'dual' transplant into a single recipient for moderate damage on biopsy.[8,9] In a prospective (non-randomised) cohort study,[10] Remuzzi et al. reported that adoption of this system resulted in a 21% improvement in three-year graft survival.

Notwithstanding, pre-implantation biopsy remains one of the most contested issues in clinical transplantation. Only about half of published studies confirm an association with implantation biopsy analysis and kidney graft outcome,[11] possibly reflecting: sampling error from differences in the type and quality of biopsy[12–14]; uncertainty over the specific anatomical features that predict early graft loss[15,16]; or inconsistencies in the initial histopathological assessment.[17] Pre-implantation biopsy may therefore lead to unnecessary discard of kidneys that would otherwise have provided acceptable transplant function.[18,19] However, these subsequent publications have been retrospective single-centre or registry analyses, and hence the true impact of pre-implantation biopsy remains unclear.

Only one of the 23 UK kidney transplant units, the Cambridge Transplant Unit, has introduced routine pre-implantation biopsy analysis of elderly deceased donor kidneys. In addition to reporting that the Remuzzi classification is as applicable to elderly donation after circulatory death (DCD) kidneys as donation after brain death (DBD) kidneys,[20,21] their retrospective analyses suggest that the use of pre-implantation biopsy resulted in increased numbers of kidney transplants from elderly DCD donors,[22] with reduced waiting times for elderly listed recipients.[23]

Offering of all UK deceased donor kidneys is coordinated centrally through the NHS Blood and Transplant (NHSBT) UK Kidney Offering Scheme.[24] This infrastructure enabled formal trial introduction of a National Digital Pathology Service (NDPS) that provided access to urgent pre-implantation biopsy analysis to the 22 remaining UK transplant centres. Thus, using a Stepped Wedge Cluster Randomised Controlled Trial

(SWCRCT) design, and relying on outcome data already mandated for return to the NHSBT UK Transplant Registry (UKTR), the PITHIA trial (Pre-Implantation Trial of Histopathology In renal transplant Allografts[25]) tested the hypothesis that pre-implantation biopsy availability would increase the number, and/or improve the function, of kidney transplants performed from elderly deceased donors in the UK.

Here we report the results of this trial.

Methods

Trial design

The impact of introduction of the NDPS on UK kidney transplant numbers and outcomes was trialled prospectively, using a SWCRCT design, with the trial commencing on 1st October 2018 and ending on 31 January 2022, after being paused for 15 months (21 March 2020–20 July 2021) during the Covid-19 pandemic. Accordingly, over a 24-month study period, at 4-monthly intervals, randomly determined groups of 4 or 5 UK kidney transplant centres (clusters) were randomised to the intervention, such that by trial completion, all 22 participating centres had access to the biopsy service (Fig. 1a). Centres were given three months' notice of their cross-over date.

Standard of care (control)

There are 23 adult kidney transplant centres in the UK and all deceased donor kidneys are offered to the top-ranked individuals identified by the national offering algorithm, based upon waiting time, HLA-match, donor-recipient age-matching and location matching[24]—please see Supplementary Methods for more detail. At trial commencement, only the Cambridge Transplant Unit had access to urgent pre-implantation biopsy analysis, and did not participate because it was beyond clinical equipoise. For the remaining centres, decisions to accept and transplant offered deceased donor kidneys were based upon consideration of the donor and recipient history, and macroscopic appearances of the kidney.

Intervention condition

Upon receiving access to the NDPS service, implanting centres could request, at the time of kidney offering, urgent pre-implantation kidney biopsy from deceased UK donors aged 60 years or over. A punch biopsy was taken at retrieval by the surgical retrieval team, the paraffin embedded block processed at one of 6 national histopathology centres, and digitally scanned images transmitted electronically to one of 12 consultant renal histopathologists, who reported the extent of chronic injury using a modified 'Remuzzi' score.[20] A report was issued to the implanting surgical team, alongside implantation advice: use singly; perform a dual transplant; or discard both kidneys, depending on the total Remuzzi score.

All centres received in-person training prior to biopsy access (prior to the pandemic, virtual training following trial restart), and at least one follow-up virtual meeting one month after gaining access to the service. All kidneys meeting the inclusion criteria during the study period (those offered from deceased UK donors aged 60 years or over) were enrolled in the trial through central organ offering and data collection at NHSBT. Patient outcomes were obtained from the UKTR held by NHS Blood and Transplant, 12 months after transplantation.

Ethical approval

Trial Registration Number: ISRCTN 11708741.

The Cambridge South Research Ethics Committee (REC) provided a favourable ethical opinion, and approval was granted by the Health Research Authority on the 18th Jan 2018 (REC reference 17/EE/0481; IRAS project ID 226412). The REC confirmed that individual recipient consent for trial participation was not required (as we were trialling introduction of a clinical service), but consent for transplantation was taken by discussing the biopsy results, along with the potential risks and benefits of the offered kidney. Transplant centres' participation was covered by site-specific approvals. Trial management was provided by the trial managers (EL and AS) and by the trial management group, with oversight by independent trial steering and data management committees.

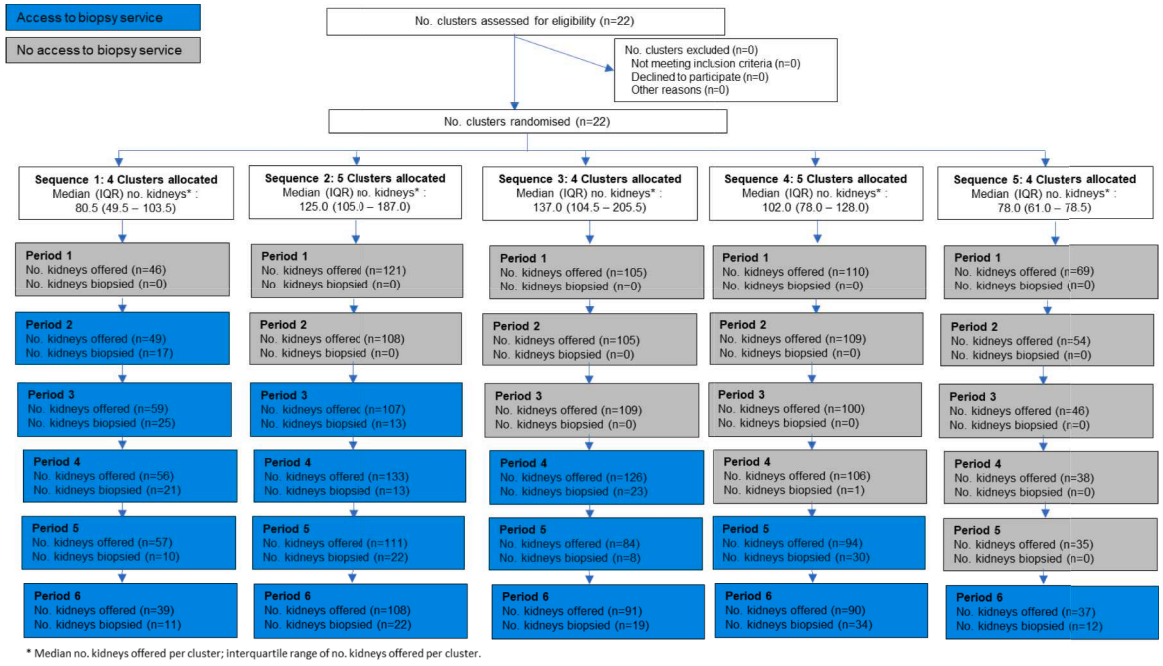
Trial outcomes

There were two co-primary outcomes: the proportion of eligible kidneys that were transplanted from deceased donors aged 60 years or older; and, for those kidneys transplanted, the eGFR of the recipient at one year after transplant.

The first primary end-point considered whether the kidney was *first* offered to a centre with biopsy access (FOY) or whether it was *first* offered to a centre without biopsy access (FON). However, upon decline by the centre responsible for the first named recipient, deceased donor kidneys were offered sequentially to the next ranked recipients according to the NHSBT UK Kidney Offering Scheme, with the schedule of the stepped wedge cluster design determining each centre's ability to request a pre-implantation biopsy. To capture the sequential nature of offering, for the second primary endpoint, we analysed one-year eGFR of all study kidneys transplanted with biopsy status designated by whether the implanting centre had access (TxY) or not (TxN) to the NDPS.

The trial secondary outcomes are detailed in the Supplementary Methods, and include, among other metrics: the 1-year eGFR for kidneys transplanted upon first offer; the proportion of kidneys transplanted according to whether the implanting centre had access to biopsy or not; the total number of study kidney

a



b

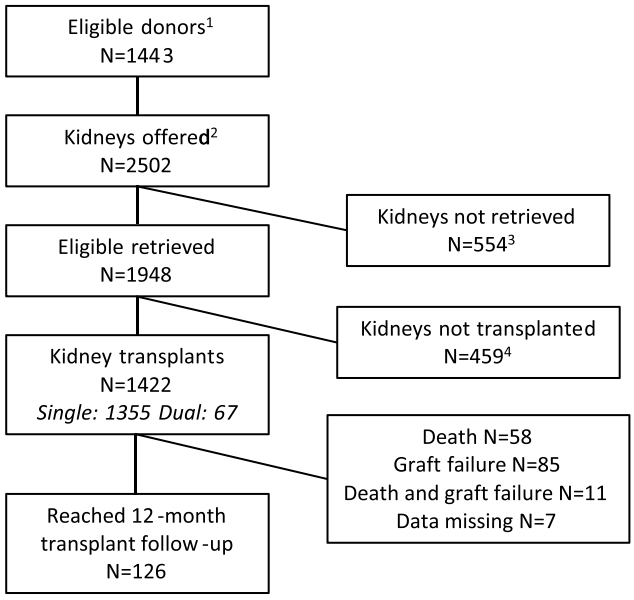


Fig. 1: **Pithia trial: stepped wedge cluster randomised controlled trial. a)** Stepped wedge cluster consort diagram. All 22 UK kidney transplant centres (clusters) enrolled in the study (other than Cambridge, who was deemed beyond clinical equipoise). Groups of 4 or 5 centres were randomised to receive access to the biopsy service at 4 monthly intervals, with columns showing biopsy access for each group (sequence) according to trial period (rows). Kidneys were the entity analysed, and upon decline could be offered sequentially to multiple clusters (and hence sequences), but Figure 1 depicts only the first centre/cluster to which each kidney was offered. Hence each kidney will appear in one period and one sequence only. **b)** Kidney eligibility flow chart. [1]Eligible donors are those aged ≥60 years old with consent for donation. [2]The deficit in the number of kidneys offered (n = 2502) compared to the initial number of eligible kidneys (n = 2882) reflects circulatory death donors that did not proceed to organ retrieval because of prolonged time to asystole after withdrawal of life-supporting treatment. [3]Kidneys were not retrieved if declined by all centres in advance of donation. [4]This number includes 46 study kidneys that were declined upon offering to the participating centres, before being transplanted at Cambridge.

transplants performed; 12 month patient and graft transplant survival; incidence of kidney primary non-function; the number of single and dual transplants performed; the median number of centres to which each study kidney was offered; proportion of kidneys biopsied by centres with access to the biopsy service; biopsy fidelity (whether the biopsy report recommendations were observed); and the US Kidney Donor Risk Index and Kidney Donor Profile Index of the biopsied kidneys.[26] These secondary outcomes were selected to examine outcomes for the transplanted kidneys other than one-year eGFR and to assess how the different centres adopted the biopsy service; all planned secondary outcome analyses are reported. The subgroup analyses, such as the comparison of DBD vs. DCD kidneys, are also detailed in the Supplementary Methods. All secondary outcome measures are reported in this manuscript, as detailed in Table X1, Supplementary Methods.

Statistical analysis

A restricted randomisation technique was used to randomly allocate the clusters to their cross-over date. The within-period intra-cluster correlation (WP-ICC) and cluster autocorrelation (CAC) for the two primary outcomes were calculated by developing generalised linear mixed models, using offering and transplant data extracted from the UKTR for the 2 years prior to trial commencement. A standard variance components structure was assumed, and the WP-ICC was assumed constant (block-exchangeable structure). These correlation estimates were then applied to produce power curves based on 20 clusters (to allow for cluster level attrition) over a period of 24 months, using methodology proposed by Hooper et al.[27] and Hooper and Bourke[28]; further details are provided in the Supplementary Methods. For primary outcome 1—the proportion of kidneys transplanted on first offer; assuming 2102 eligible kidneys would be offered to 20 clusters (centres) over the 24-month study period, the trial would provide 85% power (for a significance level of 2.5%) to detect a clinically important 11% increase in acceptance of first offers from 28% to 39%. For primary outcome 2—eGFR measurement one year after transplant; the assumption that 960 eligible study kidneys would be transplanted by 20 participating centres would provide 89% power at the 2.5% significance level to detect a clinically important increase of 6 ml/min in one-year eGFR. Full details and sensitivity to assumptions are provided in the Supplementary Methods.

The statistical analysis plan is described in detail in the Supplementary Methods. Briefly, depending on outcome studied, logistic or binomial (with identity link) mixed effects regression models were fitted, adjusting for clustering and fixed period effects to reflect the stepped-wedge nature of the design. The main analysis was by intention to treat. A 2.5% significance level was used for each of the two primary outcomes, and 97.5% confidence intervals are presented for estimates of treatment effect; 95% confidence intervals are presented for other outcomes. We report (adjusted) odds ratios and risk differences for binary outcomes, and mean differences for continuous outcomes. Sensitivity, subgroup, and post-hoc analyses are also detailed in the Supplementary Methods.

Role of the funding source

The funder, NIHR, was not involved in data collection, data analysis and interpretation, nor in the writing of the report or the decision to submit the paper for publication. Minor modifications to trial design were made following external peer review upon initial grant application.

Results

Participant flow

The 22 participating UK kidney transplants centres transitioned to the NDPS service according to the planned SWCRCT schedule (Fig. 1a), although the trial and the NDPS was paused for 16 months during the SARS-CoV-2 pandemic (see Supplementary Methods). During the trial, 2502 eligible kidneys from deceased donors ≥60 years old were offered to the 22 centres (Fig. 1b). Of these, 1241 were first offered to a centre with biopsy access (FOY), and 1261 were first offered to a centre without biopsy access (FON). The 2502 study kidneys were offered to a median of 2 different centres (8877 offers in total).

Baseline characteristics

The baseline donor characteristics for the offered kidneys are shown in Table 1, with the breakdown of these offers to each detailed in Table s1. Median (IQR) donor age for the two groups was similar (FOY; 68 (63–72) years: FON; 68 (63–73)), with numbers of DCD donors exceeding those of DBD donors (1362/2502 (54.4%) vs. 1140/2502 (45.6%)), but with similar proportions of each in the FOY and FON groups. The incidence of donor diabetes, hypertension and cardiovascular disease was also comparable between the two groups. Donor demographics were also broadly similar for each group of centres receiving access during the different trial periods (Table s2). Study kidneys were implanted into generally elderly recipients (median (IQR) recipient age of all recipients: 63 (56–69) years), but otherwise recipient demographics were similar for the two cohorts (Table s3).

Transplant rates of offered kidneys according to centre biopsy status

With regards the first primary outcome, 672/2502 (26.9%) study kidneys were transplanted upon first

offer, with possibly a lower proportion of the FOY cohort transplanted (295 of 1241, 23.8%) than of the FON cohort (377 of 1261, 29.9%), although this was not statistically significant (adjusted OR (97.5% CI); 0.91 (0.60–1.39); p = 0.6083: Table 2). Subgroup analysis of DBD donors, DCD donors, or of offers from deceased donors over 70 years old similarly did not reveal a significant difference between the FOY and FON cohorts (Table 2), although for DCD donors, only 127 of 669 (19.0%) kidney offers were transplanted in the FOY cohort, compared to 216 of 693 (31.2%) in the FON cohort. A similar non-significant result was found when performing sensitivity analyses that considered the potential learning phase immediately after access to the biopsy service, or with covariate adjustment for donor factors (not shown).

Overall, 1422 of the 2502 study kidneys (56.8%) were transplanted, reflecting the sequential offering of kidneys upon decline by the first-offered centre (Fig. 1b). Secondary outcome analysis revealed that, of the 1170 kidneys offered last to a centre with biopsy access (TxY), 659 (56.3%) were transplanted, with 31 (4.7%) of these performed as dual kidney transplants (Table 3). A comparable proportion of the kidneys offered last to centres *without* biopsy capacity (TxN) were transplanted (763 of 1332 kidneys (57.3%: adjusted Odds Ratio (95% CI) 0.99 (0.70–1.42); p = 0.9770)), with 36/763 (4.7%) as dual transplants.

Donor characteristic	First offered centre could not request biopsy (no. offered kidneys = 1261)	First offered centre could request biopsy (no. offered kidneys = 1241)	Total (no. offered kidneys = 2502)
Age	68 (63–73)	68 (63–72)	**68 (63–72)**
Sex[a]			
Male	633/1261 (50.2)	663/1241 (53.4)	**1296/2502 (51.8)**
Female	628/1261 (49.8)	578/1241 (46.6)	**1206/2502 (48.2)**
Ethnicity			
Asian	34/1246 (2.7)	23/1224 (1.9)	**57/2470 (2.3)**
Black	9/1246 (0.7)	11/1224 (0.9)	**20/2470 (0.8)**
Mixed	10/1246 (0.8)	5/1224 (0.4)	**15/2470 (0.6)**
White	1185/1246 (95.1)	1181/1224 (96.5)	**2366/2470 (95.8)**
Other	8/1246 (0.6)	4/1224 (0.3)	**12/2470 (0.5)**
Creatinine[b] (μmol/L)	65 (52–84)	64 (51–82)	**64 (52–83)**
Donor type			
DBD	568/1261 (45.0)	572/1241 (46.1)	**1140/2502 (45.6)**
DCD	693/1261 (55.0)	669/1241 (53.9)	**1362/2502 (54.4)**
Cause of death			
CVA	778/1261 (61.7)	805/1241 (64.9)	**1583/2502 (63.3)**
RTA	7/1261 (0.6)	6/1241 (0.5)	**13/2502 (0.5)**
Other trauma	16/1261 (1.3)	6/1241 (0.5)	**22/2502 (0.9)**
Miscellaneous	460/1261 (36.5)	424/1241 (34.2)	**884/2502 (35.3)**
Blood group			
O	604/1261 (47.9)	582/1241 (46.9)	**1186/2502 (47.4)**
A	519/1261 (41.2)	485/1241 (39.1)	**1004/2502 (40.1)**
B	98/1261 (7.8)	131/1241 (10.6)	**229/2502 (9.2)**
AB	40/1261 (3.2)	43/1241 (3.5)	**83/2502 (3.3)**
History of hypertension	647/1247 (51.9)	655/1217 (53.8)	**1302/2464 (52.8)**
History of diabetes	161/1252 (12.9)	167/1220 (13.7)	**328/2472 (13.3)**
History of cardiac disease	295/1241 (23.8)	273/1225 (22.3)	**568/2466 (23.0)**
History of smoking	774/1257 (61.6)	746/1240 (60.2)	**1520/2497 (60.9)**

Data are n/N (%) for categorical variables and median (IQR) for continuous variables. *Summary of missing data:* Ethnicity is missing for 32 donors. Creatinine is missing for 87 donors. History of hypertension is missing for 38 donors. History of diabetes is missing for 30 donors. History of cardiac disease is missing for 36 donors. History of smoking is missing for 5 donors. Age, sex, type, cause of death, and blood group is missing for 0 donors. DBD = Donation after Brain Death, DCD = Donation after Circulatory Death, CVA = Cerebral Vascular Accident, RTA = Road Traffic Accident, IQR = Interquartile Range. [a]Recorded on the UK Transplant Registry by Specialist Nurses in Organ Donation after referring to patient medical notes and clarification with the donor family. Donor sex reflects sex registered at birth. [b]Last reported value prior to donation. Donors will appear in this table more than once if they donated two kidneys.

Table 1: **Donor characteristics by arm.**

Function and one-year outcomes of transplanted study kidneys

Table 4 presents the second primary outcome and shows that the adjusted mean 12-month eGFR (SE) was similar for the TxY and the TxN cohorts (43.7 (1.3) ml/min/1.73 m^2 vs. 42.2 (1.3) ml/min/1.73 m^2; p = 0.3726). Subgroup analysis of DBD donors, DCD donors, or of transplants from deceased donors over 70 years old reached similar conclusions (Table 4). Likewise, sensitivity analysis involving imputation of missing 12-month eGFR values (due to lack of return data from centre or to patient death/graft failure) did not alter findings (not shown). Again, a non-significant result was found when performing sensitivity analyses that considered covariate adjustment for donor and recipient factors, the early 'learning' phase of the biopsy service, and per protocol (PP) analysis (not shown). The incidence of primary non-function (21 of 647; 3.2% vs. 24 of 753; 3.3%), delayed graft function (169 of 626; 27% vs. 175 of 729; 24%), and 12-month graft (both 93%) and recipient (95% vs. 94%) survival was also similar for kidneys transplanted in centres that had access to the biopsy service, compared to kidneys transplanted at centres that had not yet received access (Table s4, Figure s1).

Considering the sub-group of kidneys that were transplanted upon *first offer*, the adjusted mean (SE) 1-year eGFR for the 295 kidneys transplanted by centres with biopsy access was 43.8 (1.9) ml/min/1.73 m^2, which is comparable to adjusted eGFR for the 377 kidneys transplanted by centres without biopsy access (42.8 (1.9) ml/min/1.73 m^2; adjusted mean difference (95% CI) 0.97 (–3.68 to 5.61); p = 0.6819; Table s5).

Uptake and use of the biopsy service

The primary outcomes selected for the PITHIA trial reflected the principal question how introduction of a NDPS impacted upon UK kidney transplant numbers and outcomes. However, we also sought to assess how the biopsy service was used, because this would determine the overall national impact. Of the 1493 kidneys offered at some stage to a centre with access to the

Outcome	First offered centre could not request biopsy (no. kidneys offered = 1261)	First offered centre could request biopsy (no. kidneys offered = 1241)	Overall (no. kidneys offered = 2502)	p-value
Primary analysis–1st primary outcome				
Kidneys transplanted on first offer–n/N (% of kidneys offered)	377/1261 (29.9)	295/1241 (23.8)	**672/2502 (26.9)**	
Adjusted[a] odds[d] ratio[e] (97.5% CI)		0.91 (0.60–1.39)		0.6083
Adjusted[c] risk difference[g] (97.5% CI)		−0.01 (−0.08 to 0.06)		
DBD donors only				
Kidneys transplanted on first offer–n/N (% of kidneys offered)	161/568 (28.3)	168/572 (29.4)	**329/1140 (28.9)**	
Adjusted[a] odds[d] ratio[e] (97.5% CI)		1.12 (0.68–1.85)		0.6062
Adjusted[b] risk difference[f] (97.5% CI)		0.02 (−0.08 to 0.12)		
DCD donors only				
Kidneys transplanted on first offer–n/N (% of kidneys offered)	216/693 (31.2)	127/669 (19.0)	**343/1362 (25.2)**	
Adjusted[a] odds[d] ratio[e] (97.5% CI)		0.76 (0.42–1.38)		0.2942
Adjusted[c] risk difference[g] (97.5% CI)		0.00 (−0.09 to 0.10)		
Donors aged >70 years				
Kidneys transplanted on first offer–n/N (% of kidneys offered)	93/468 (19.9)	77/437 (17.6)	**170/905 (18.8)**	
Adjusted[a] odds[d] ratio[e] (97.5% CI)		1.06 (0.54–2.10)		0.8378
Adjusted[c] risk difference[g] (97.5% CI)		0.03 (−0.08 to 0.15)		

DBD = Donation after Brain Death, DCD = Donation after Circulatory Death, CI = Confidence Interval. [a]Adjusted for cluster (random effect), period (fixed effect), cluster*period interaction (random effect), Covid-19 indicator (fixed effect). [b]Adjusted for cluster (random effect), period (fixed effect), Covid-19 indicator (fixed effect). [c]Adjusted for cluster (fixed effect), period (fixed effect), Covid-19 indicator (fixed effect). [d]Odds represent the odds of transplant. [e]Access to biopsy service relative to no access to biopsy service, from a mixed logistic regression model. p-value from the F-test for the treatment term from the model. [f]Access to biopsy service relative to no access to biopsy service, from a mixed binomial model with identity link. [g]Access to biopsy service relative to no access to biopsy service, from a binomial model with identity link.

Table 2: **Proportion of kidneys that are transplanted on first offer.**

biopsy service, 287 biopsies were requested (19.2%), with the majority (170 of 283; 60.1%) requested by the first centre receiving the kidney offer, and with 19.1% (54/283) and 9.5% (27/283) of biopsies requested by the 2nd and 3rd centres, respectively, to receive the kidney offer.

The US Kidney Donor Risk Index and Kidney Donor Profile Index of the biopsied kidneys (a marker of their 'quality') were similar to that of the kidneys that were not biopsied (either because offered centres did not have access to the biopsy service, or because biopsy was not requested). However, post-hoc analyses revealed that donors of the biopsied cohort were slightly older, and had a higher proportion of diabetes (Table s6), possibly suggesting that centres selected the organs perceived more 'marginal' for biopsy. A higher proportion of DBD kidneys were biopsied than DCD kidneys (157 of 1140; 13.8% vs. 130 of 1362; 9.5% of offers).

Of the biopsied kidneys, 191 of 287 (66.6%) were transplanted; and although differences in the group sizes prohibit formal statistical comparison, this proportion compares favourably to transplant rates of kidneys that were only offered to centres without biopsy capacity (643 transplants of 1009 offers (63.7%)) or offered to at least one centre with biopsy capacity but not biopsied (588 transplants of 1206 offers (48.8%)). Fourteen biopsied kidneys were transplanted by centres that had not requested the biopsy. The 'Remuzzi' biopsy scores and implantation decisions for the biopsied kidneys are detailed in Table s7. Despite a favourable biopsy score that would commend implantation as a single transplant being reported for 232 (81.4%) of the 285 biopsies (where biopsy data were reported), 59 (25.4%) were discarded, and 12 (5.2%) transplanted as dual transplants. Overall, 174 of the biopsied kidneys were implanted according to the biopsy report recommendations; a fidelity of 61.1% (174/285). Interestingly, 46 of the 100 (46%) kidneys that were biopsied on first offer were transplanted, whereas for the contralateral kidneys from the same donors that were not biopsied, only 20/100 (20%) were transplanted on first offer (aOR (95% CI) 3.43 (1.45–8.11); p = 0.0015).

During the trial, there were no reported biopsy-related complications, and no other adverse events. The unadjusted mean (SD) cold ischaemic time for the TxY cohort was 14.0 (4.7) hours, compared to 12.6 (4.1) hours for the TxN cohort, with an adjusted mean difference of 0.73 h (95% CI: −0.08 to 1.53; p = 0.0752).

Post-hoc analysis was performed to examine the relationship between the Remuzzi score and the adjusted mean one-year eGFR for the biopsied kidneys that were transplanted (Table s8). The mean (SE) one-year eGFR of all transplanted, biopsied kidneys was 41.8 (1.33) ml/min/1.73 m^2. The adjusted mean one-year eGFR of the kidneys transplanted with a biopsy score of 0 or 1 was slightly higher than for those scoring either 2 or 3–4, with the confidence intervals for the adjusted mean difference for both falling below 0. The

Outcome	*Last* offered centre could not request biopsy (no. offered kidneys = 1332)	*Last* offered centre could request biopsy (no. offered kidneys = 1170)	Overall (no. offered kidneys = 2502)	p-value
Proportion of kidneys utilised				
Kidneys transplanted[a]–n/N (% of kidneys offered)	763/1332 (57.3)	659/1170 (56.3)	**1422/2502 (56.8)**	
Adjusted[b] odds[d] ratio[f] (95% CI)	0.99 (0.70–1.42)			0.9770
Adjusted[c] risk difference[g] (95% CI)	−0.02 (−0.09 to 0.05)			
Number and proportion of 'single' vs. 'dual' kidney transplants performed				
Number of single kidney transplants–n/N (% of kidney transplants)	727/763 (95.3)	628/659 (95.3)	**1355/1422 (95.3)**	
Number of dual kidney transplants–n/N (% of kidney transplants)	36/763 (4.7)	31/659 (4.7)	**67/1422 (4.7)**	
Adjusted[b] odds[e] ratio[f] (95% CI)	0.72 (0.22–2.42)			0.5935
Adjusted[c] risk difference[h] (95% CI)	−0.02 (−0.12 to 0.09)			

[a]If an offer of a pair of eligible kidneys resulted in a dual kidney transplant, then one of the kidneys was counted as being transplanted and the other as not transplanted. [b]Adjusted for cluster (random effect), period (fixed effect), cluster*period interaction (random effect), Covid-19 indicator (fixed effect). [c]Adjusted for cluster (random effect), period (fixed effect), Covid-19 indicator (fixed effect). [d]Odds represent the odds of transplant. [e]Odds represent the odds of receiving a single kidney transplant, as opposed to dual, for transplanted patients. [f]Access to biopsy service relative to no access to biopsy service, from a mixed logistic regression model. p-value from the F-test for the treatment term from the model. [g]Access to biopsy service relative to no access to biopsy service, from a mixed binomial model with identity link. [h]Access to biopsy service relative to no access to biopsy service, from a binomial model with identity link.

Table 3: **Proportion of kidneys transplanted.**

eGFR of kidneys scoring 5–6 or 7 was perhaps higher than anticipated but there were small numbers of transplants in these groups, which is reflected in the wide confidence intervals, and a higher proportion were implanted as dual transplants.

Fidelity to the biopsy service

Finally, further post-hoc analyses were performed to assess how the observed trial primary outcomes had been influenced by the individual centres' adoption of the biopsy service. Table s9 details the numbers of first-offered study kidneys to each of the 22 participating UK transplant centres, and the transplant rates of these offers before and after access to the biopsy service. Although the number of first offers received at each centre is relatively small, and varies according to the size of that centre's waiting list, it is striking that the proportions of offers that were transplanted before and after access to the biopsy service differs between centres, with some showing marked increases in utilisation, and others marked decreases, upon receiving biopsy capacity. The proportion of biopsies requested of these first-offered kidneys also varied between centres (from 1.3% to 33.3% (Table s9)), but without a clear correlate to transplant rates. Similarly marked inter-centre variations in the proportion of eligible kidneys biopsied and in organ utilisation were evident when including in the analysis all sequential offers made to different centres for each kidney (Table s10). Despite the inter-centre variations in practice, but consistent with the response to first-offered kidneys, overall utilisation rates of DCD kidneys were poorer than DBD kidneys (624 of 1362 (45.8%) offers vs. 798 of 1140 (70.0%)), and although not formally addressed by the trial design, implantation rates for DCD kidneys, if anything, fell after centres received access to the biopsy service (Table s11).

Discussion

Pre-implantation biopsy analysis remains one of the most controversial topics in renal transplantation. Although the landmark Remuzzi study[10] reported significantly better three-year outcomes for kidneys transplanted according to pre-implantation biopsy analysis, the practice has been adopted variably, both at national and international level, with approximately 90% of kidneys in the United States with Kidney Donor Profile Indices >70% undergoing biopsy,[19] while relatively few biopsies are performed in Europe. Analysis of differing practices between France and the United States has reinforced that pre-implantation biopsy may not accurately reflect the overall 'quality' of the kidney, and results in unnecessary discard of kidneys that would have otherwise provided satisfactory function.[29] This is particularly concerning, given the anticipated global increase in incidence of end-stage kidney disease,[6] with the requirement for transplantation in the elderly predicted to increase by as much as four-fold in the UK in the next decade.[3] The recognition that a large proportion of kidneys from consenting elderly deceased donors are ultimately not transplanted, allied to feedback from the UK transplant centres that urgent histopathology availability would allow their more effective use of this cohort, prompted this randomised trial evaluation of the introduction of a NDPS for transplantation; we believe the first of its kind worldwide.

The optimal design for trialling implementation of a national histopathology service generated much discussion. We discounted a standard randomised trial in which one kidney of a pair from a deceased donor was randomly offered with biopsy availability, because the offer of biopsy information for the one kidney was likely to 'contaminate' (i.e., change) implantation practice of the paired kidney offered without biopsy. Instead, a SWCRCT approach was chosen, because clusters serve

Outcome	Transplanting centre could not request biopsy (no. transplants = 763)	Transplanting centre could request biopsy (no. transplants = 659)	Overall (no. of transplants = 1422)	p-value
Primary analysis–2nd primary outcome				
12-month eGFR (ml/min/1.73 m^2)				
Number of patients surviving to at least 10 months	657	517	**1174**	
Patients with 12-month eGFR recorded–n/N (% of those surviving to at least 10 months)	607/657 (92.4)	486/517 (94.0)	**1093/1174 (93.1)**	
Unadjusted mean (SD) eGFR	40.8 (16.1)	43.0 (17.0)	**41.8 (16.5)**	
Adjusted[a] mean (SE) eGFR	42.2 (1.3)	43.7 (1.3)		
Adjusted[a] mean difference (97.5% CI)	1.53 (−2.33 to 5.40)			0.3726
DBD donors only				
Number of patients surviving to at least 10 months	347	316	**663**	
Patients with 12-month eGFR recorded–n/N (% of those surviving to at least 10 months)	320/347 (92.2)	294/316 (93.0)	**614/663 (92.6)**	
Unadjusted mean eGFR (SD)	41.4 (16.7)	44.0 (17.7)	**42.6 (17.2)**	
Adjusted[a] mean (SE) eGFR	44.3 (1.8)	46.4 (1.7)		
Adjusted[a] mean difference (97.5% CI)	2.10 (−3.13 to 7.32)			0.3663
DCD donors only				
Number of patients surviving to at least 10 months	310	201	**511**	
Patients with 12-month eGFR recorded–n/N (% of those surviving to at least 10 months)	287/310 (92.6)	192/201 (95.5)	**479/511 (93.7)**	
Unadjusted mean (SD) eGFR	40.2 (15.3)	41.4 (15.9)	**40.7 (15.5)**	
Adjusted[a] mean (SE) eGFR	38.4 (1.9)	39.9 (1.9)		
Adjusted[a] mean difference (97.5% CI)	1.46 (−3.98 to 6.89)			0.5459
Donors aged >70 years				
Number of patients surviving to at least 10 months	199	128	**327**	
Patients with 12-month eGFR recorded–n/N (% of those surviving to at least 10 months)	186/199 (93.5)	119/128 (93.0)	**305/327 (93.3)**	
Unadjusted mean (SD) eGFR	39.4 (14.1)	38.7 (17.5)	**39.1 (15.5)**	
Adjusted[b] mean (SE) eGFR	39.9 (2.5)	41.0 (2.7)		
Adjusted[b] mean difference (97.5% CI)	1.09 (−6.58 to 8.75)			0.7498

DBD = Donation after Brainstem Death, DCD = Donation after Circulatory Death, SD = Standard Deviation, SE = Standard Error, CI = Confidence Interval. [a]Mixed normal linear regression model adjusted for cluster (random effect), period (fixed effect), Covid-19 indicator (fixed effect). [b]Normal linear regression model adjusted for cluster (fixed effect), period (fixed effect), Covid-19 indicator (fixed effect). p-value from the F-test for the treatment term from the model.

Table 4: **12-month estimated Glomerular Filtration Rate (eGFR) for all transplanted kidney.**

as their own control, allowing more heterogeneity within clusters than trials with parallel randomisation, and because, as transplant practice continues to evolve, the stepped-wedge design enables such changes occurring during the trial period to be incorporated into the analysis.[30] Perhaps most crucially, this approach allowed all centres access to the service, and following patient and public engagement, the trial management committee thought it important that all UK listed transplant recipients would potentially benefit from the service, rather than being disadvantaged geographically. Finally, by enabling a staggered introduction of the intervention across the UK, the stepped-wedge approach provided the trial group the necessary time to provide a tailored education programme to each participating centre.

To address criticisms regularly levied against practical aspects of pre-implantation biopsy analysis, we aimed to introduce an NDPS that would be considered 'gold-standard'. Thus, all biopsies were formalin-fixed and paraffin-embedded, with processing and staining at each of the 6 histopathology centres performed according to standardised trial protocol. Similarly, all UK National Organ Retrieval Teams received training and regular feedback on performing 4 mm punch biopsies on retrieved kidneys, with punch biopsies chosen over wedge or needle biopsy because of preliminary assessment on discarded kidneys indicating that this approach provided the best quality biopsy, with least user variability. Finally, at trial onset, the team of consultant renal histopathologists reviewed a training set of historical biopsy images, with good concordance (see Supplementary Methods) achieved between the different histopathologists. It is perhaps therefore surprising that the trial failed to show significant differences in either of the primary endpoints—the proportion of offered elderly deceased donor kidneys that were transplanted and their eGFR at one year—upon centres gaining access to the biopsy service.

There are several limitations to our study. Firstly, acceptance of first-offered kidneys was chosen as the primary end-point for assessing the impact of biopsy on utilisation, whereas arguably overall utilisation, irrespective of offering sequence, is perhaps more relevant. This was, however, assessed as a secondary end-point, and our analysis suggests that although 70% of study kidneys were offered to at least one centre with biopsy provision, this did not impact on kidney utilisation nationally. Although this sequential offering of declined kidneys, particularly the policy of making biopsy results available when kidneys were re-offered, risked contamination of the trial arms, such cross-over happened infrequently. Only 14 biopsied kidneys were implanted by a centre that did not request the biopsy, and only two of the 763 kidneys implanted by centres without access to biopsy (the TxN cohort) had been biopsied prior to re-offering. A further limitation was the necessity to suspend the trial for 16 months during the COVID-19 pandemic, and although sensitivity analyses suggest this did not influence trial outcomes, national waiting lists and transplant activity were profoundly affected by the pandemic and it's possible that subtle changes to the UK transplant landscape (either in listing criteria or in selection of organs for transplantation) persisted after trial resumption.

Perhaps the greatest limitation is the inability to comment decisively on the reasons why introduction of the NDPS did not impact upon overall kidney transplant numbers. The trial was not designed to assess this, but we think it important to stress that its outcomes do not necessarily indicate that pre-implantation biopsy analysis is ineffective. Certainly, the frequently raised concern that biopsy analysis leads to unnecessary kidney discard does not appear to have been borne out by our trial data. Two-thirds of biopsied kidneys were transplanted, which represents a slightly higher utilisation rate than for kidneys for which biopsy was either unavailable or not performed, with 1-year eGFR of the transplanted, biopsied kidneys acceptable clinically. Biopsy was not mandated, and thus there may have been a bias to selecting only kidneys for biopsy that the centre were intending to implant. However, kidneys that were biopsied tended to be from more elderly donors and from those with a higher incidence of diabetes, so it does not seem that the biopsy service was used to provide reassurance for those kidneys that were already likely to be transplanted. In support, utilisation rates for those kidneys with more substantial chronic injury revealed on biopsy (Remuzzi scores > 4) were much lower (around 30%), and transplant rates on first offer were twice that for kidneys where one of the pair was biopsied and the contralateral kidney from the same donor not biopsied (40% vs. 20%). The proportion of biopsied kidneys that were transplanted could possibly have been higher still, in that approximately a quarter of kidneys with favourable biopsy results were discarded. This presumably reflects that the biopsy result was not considered in isolation, but in concert with other less favourable indices, such as the donor history and macroscopic appearance of the kidney.

In any event, the impact of performing a biopsy on trial outcomes is overshadowed by the very much larger cohort of kidneys that were offered to centres with biopsy capacity, but for which biopsy was not requested. Biopsies were requested for only a fifth of kidneys that were offered to at least one centre with access to the service, but those kidneys that were not biopsied were still classified in the access to biopsy arm for analysis of trial outcomes. The donor characteristics of the kidneys offered to centres with biopsy capacity were similar to those only offered to centres without biopsy availability, and it is not immediately obvious why transplant rates for the latter cohort (643 of 1009 offers; 63.7%) are greater than for kidneys offered and not biopsied, despite the potential to do so (588 of 1206 offers; 48.8%). It is striking, however, that transplant rates for the trial DBD kidneys were much greater than for the DCD cohort, with a higher proportion of DBD kidney offers biopsied than DCD kidney offers, and with implantation rates for DCD kidneys, if anything, falling after centres received access to the biopsy service. Thus, it appears that access to the biopsy service did not overcome some clinicians' reluctance to accept elderly DCD kidney offers; indeed, an unforeseen consequence may have been that centres focused on the potential to accept and biopsy DBD kidney offers at the expense of accepting DCD offers. This may reflect concerns that biopsy would result in cold ischaemic times that are prohibitively long for DCD, but not DBD, kidneys, even though analysis of long-term follow-up of large numbers of UK DCD kidney transplants confirms very similar outcomes for age-matched DBD kidneys.[7]

Despite these drawbacks, over the two years of the trial and with involvement of 22 of 23 UK kidney transplant units, introduction of the NDPS did not materially influence numbers of UK deceased donor kidney transplants, nor their early outcomes, with the high-levels of decline/discard of kidneys formally offered for transplantation from elderly deceased donors, particularly from DCD donors, a major concern. For other transplant programs considering introducing a pre-implantation biopsy service, our results suggest that alternative approaches, or at least additional strategies, perhaps addressing centres' behavioural intransigence, are required to enable this donor pool to be used more effectively. Conversely, however, for those countries with an established pre-implantation biopsy service, our results do not necessarily indicate that discontinuation of that service would improve organ utilisation.

Contributors

Contributions to the various aspects of the study are as detailed below. All authors had full access to the data in the study and take responsibility for the decision to submit for publication.

The trial statisticians JMehew, HThomas, RBrown, SPhillips, LSmith, and KHemming had access to, and verified, the underlying data. GJPettigrew and Dsummers recommended submission to the Lancet Regional Health, with support from all coauthors.

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Data sharing statement

Individual participant data that underlie the results reported in this article will be available, after de-identification (text, tables, figures, and appendices) to researchers who provide a methodologically sound proposal with pre-defined aims. The study protocol, statistical analysis plan and analytic code will also be available. Data will be available from three months following article. Proposals should be directed to gjp25@cam.ac.uk; to gain access, data requestors will need to sign a data access agreement. If UK Transplant Registry Data is required, additional approval from the relevant NHS Blood and Transplant research group will be sought upon receipt of a data sharing request form.

Declaration of interests

The following authors have declarations:

CBoffa has received consultancy fees from Organox Ltd and educational fees from Chiesi UK Ltd. DANeil has received travel support from Sysmex UK Ltd. FJMFDor has received speaker fees from Chiesi UK Ltd, Astellas Pharma Inc, and Sandoz UK Ltd. LMarson has received royalties from Elsevier and is a non-executive director on the NHS Blood and Transplant Board. PMark has received research grant support from AstraZeneca UK Plc and Boehringer Ingelheim Ltd, consultancy fees and honoraria from AstraZeneca UK Plc, Bayer UK, Boehringer Ingelheim Ltd, Pharmacosmos A/S, and CSL Vifor UK. He has participated on advisory boards for Vertex Pharmaceuticals and Novartis AG. RMotallebzadeh has received research grant support from Kidney Research UK. JOOAyorinde has received Research Grant support from NIHR Clinical Lectureship and AstraZeneca Global Postdoc Awards and has received an honoraria from Chiesi UK. ASidders has received funding support from NIHR grant funding awards to the NHS Blood and Transplant Clinical Trials Unit. SKnight has received royalties from Evidentia publishing, OVID, consultancy fees from Organox Ltd and stock options from OCHRE bio Ltd for consultancy work. ZMoinuddin has received honoraria from W. L. Gore & Associates and Novartis AG, and support for attending educational meetings from Inutuitive and TelBio.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2025.101390.

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