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Early ultrasound surveillance of newly-created haemodialysis arteriovenous fistula

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Complete List of Authors:	Richards, James ; Royal Free Hospital Summers, Dominic; University of Cambridge, Department of Surgery; NHS Blood and Transplant, Organ Donation and Transplantation Sidders, Anna; NHS Blood and Transplant Organ Donation and Transplantation Directorate Allen, Elisa; NHS Blood and Transplant Organ Donation and Transplantation Directorate Thomas, Helen; NHS Blood and Transplant Organ Donation and Transplantation Directorate Hossain, Mohammad; Royal Free Hospital, Transplantation Unit Paul, Subhankar; University of Cambridge Department of Surgery Slater, Matthew; Cambridge University Hospitals NHS Foundation Trust Bartlett, Matthew; Royal Free Hospital Lagaac, Regin; Cambridge University Hospitals NHS Foundation Trust Laing, Emma; NHS Blood and Transplant Organ Donation and Transplantation Directorate Hopkins, Valerie; NHS Blood and Transplant Organ Donation and Transplantation Directorate Fitzpatrick-creamer, Chloe; NHS Blood and Transplant Organ Donation and Transplantation Directorate Hudson, Cara; NHS Blood and Transplant Organ Donation and Transplantation Directorate Parsons, Joseph; NHS Blood and Transplant Organ Donation and Transplantation Directorate Turner, Samuel; North Bristol NHS Trust Tambyraja, Andrew; The University of Edinburgh Somalanka, Subash; Epsom and Saint Helier Hospital NHS Trust Hunter, James; University of Oxford Nuffield Department of Surgical Sciences, Oxford Transplant Centre Dutta, Sam; Nottingham University Hospitals NHS Trust Hoye, Neil; South Tees Hospitals NHS Foundation Trust Lawman, Sarah; Brighton and Sussex University Hospitals NHS Trust Salter, Tracey; Epsom and Saint Helier Hospital NHS Trust; Frimley Health NHS Foundation Trust Aslam, Mohammed; Imperial College Healthcare NHS Trust Bagul, Atul; University Hospitals of Leicester NHS Trust Sivaprakasam, Rajesh; Barts and The London NHS Trust Smith, George; Hull University Teaching Hospitals NHS Trust Moinuddin, Zia; Manchester Royal Infirmary, Department of Renal and

	Pancreas Transplantation Knight, Simon; University of Oxford, Nuffield Department of Surgical Sciences Barnett, Nicholas; Guy's and St Thomas' NHS Foundation Trust Motallebzadeh, Reza; UCL, Renal Medicine Pettigrew, Gavin; University of Cambridge, Department of Surgery;
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Early ultrasound surveillance of newly-created haemodialysis arteriovenous fistula

Authors

James Richards [1,2,3], Dominic Summers [1,2], Anna Sidders [4], Elisa Allen [4], Helen Thomas [4], Mohammed Ayaz Hossain [3], Subhankar Paul [1,2], Matthew Slater [1], Matthew Bartlett [3], Regin Lagaac [1], Emma Laing [4], Valerie Hopkins [4], Chloe Fitzpatrick-Creamer [4], Cara Hudson [4], Joseph Parsons [4], Sam Turner [5], Andrew Tambyraja [6], Subash Somalanka [7], James Hunter [8], Sam Dutta [9], Neil Hoye [10], Sarah Lawman [11], Tracey Salter [7,12], Mohammed Aslam [13] Atul Bagul [14], Rajesh Sivaprakasam [15], George Smith [16], Zia Moinuddin [17], Simon Knight [18], Nicholas Barnett [19], Reza Motallebzadeh [3], Gavin J Pettigrew *[1,2].

On behalf of the SONAR trial group [20].

[1] Addenbrooke's Hospital, Hill Road, Cambridge

[2] University of Cambridge, Hill Road, Cambridge

[3] Royal Free London NHS Foundation Trust

[4] NHS Blood and Transplant Clinical Trials Unit

[5] North Bristol NHS Trust

[6] Royal Infirmary of Edinburgh, NHS Lothian

[7] Epsom and St Helier University Hospitals NHS Trust

[8] University Hospital Coventry and Warwickshire NHS Trust

[9] Nottingham University Hospitals NHS Trust

[10] South Tees Hospitals NHS Foundation Trust

[11] Brighton & Sussex University Hospitals NHS Trust

[12] Frimley Health NHS Foundation Trust

[13] Imperial College Healthcare NHS Trust, London, UK

[14] University Hospitals of Leicester NHS Trust

[15] Bart's Health NHS Trust

[16] Hull University Teaching Hospitals NHS Trust

[17] Manchester University NHS Foundation Trust

[18] Oxford University Hospitals NHS Foundation Trust

[19] Guy's and St Thomas' NHS Foundation Trust

[20] See Appendix 1

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Corresponding author

Professor Gavin Pettigrew (gjp25@cam.ac.uk)

Department of Surgery, Box 202, Addenbrooke's Hospital CB2 0QQ

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Abstract

Introduction:

We assess if ultrasound surveillance of newly-created arteriovenous fistulas (AVFs) can predict non-maturation sufficiently reliably to justify randomised controlled trial (RCT) evaluation of ultrasound-directed salvage intervention.

Methods:

Consenting adults underwent blinded fortnightly ultrasound scanning of their AVF after creation, with scan characteristics that predicted AVF non-maturation identified by logistic regression modelling.

Results:

Of 333 AVFs created, 65.8% matured by 10 weeks. Serial scanning revealed that maturation occurred rapidly, whereas consistently lower fistula flow rates and venous diameters were observed in those that did not mature. Wrist and elbow AVF non-maturation could be optimally modelled from the week four ultrasound parameters alone, but with only moderate positive predictive values (wrist, 60.6% (95% CI 43.9 – 77.3); elbow, 66.7% (48.9 - 84.4)). Moreover, 40 (70.2%) of the 57 AVFs that thrombosed by week 10 had already failed by the week 4 scan, thus limiting the potential of salvage procedures initiated by that scan's findings to alter overall maturation rates.
Modelling of the early ultrasound characteristics could also predict primary patency failure at 6 months, but that model performed poorly at predicting assisted primary failure (those AVFs that failed despite a salvage attempt), partly because patency of at-risk AVFs was maintained by successful salvage performed without recourse to the early scan data.

Conclusions:

Early ultrasound surveillance may predict fistula maturation, but is likely, at best, to result in only very modest improvements in fistula patency. Power calculations suggest that an impractically large number of participants (>1700) would be required for formal RCT evaluation.

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Introduction

For most individuals with end-stage renal disease (ESRD), arteriovenous fistulas (AVFs) are the preferred modality for providing haemodialysis. Compared to dialysis via a central venous catheter (CVC), AVF use is associated with decreased hospitalisation from bloodstream infections (1-5), thereby offering substantial cost savings (6, 7), and a 40% reduction in mortality (8). Despite this, as many as two-thirds of those commencing haemodialysis in the UK do so via a CVC (9). This partly reflects that, once created, AVFs must 'mature' over several weeks before they can be used for dialysis, with approximately 30% of fistulas failing to do so (10-15). These failures necessitate either salvage interventions or creation of a new fistula, thus potentially prolonging the requirement for dialysis via a CVC. Maturation failure and early thrombosis may, moreover, limit options for future AVF creation, by precluding re-use of the entire draining fistula vein.

AVF maturation is characterised by massive increases in blood flow through the AVF and marked expansion in the fistula vein diameter, with compensatory thickening or 'arterialisation' of the vein wall. Doppler ultrasound surveillance of AVFs immediately after their creation may therefore identify early flow characteristics or anatomical features (such as the development of juxta-anastomotic ('swing-segment') stenosis (16)), that predict subsequent maturation failure. By providing an opportunity for successful radiological or surgical salvage, potentially before terminal thrombosis of the AVF, such early identification may improve overall AVF patency and lessen the requirement for dialysis via a CVC. This, however, remains largely untested. One randomised controlled trial (RCT) (13), has evaluated routine early ultrasound and reported a 13.6% fistula failure in the surveillance group, compared to 25.4% in the control group (ultrasound performed selectively, according to clinical indication), but the study was powered for a relatively large (20%) effect size, and the difference in maturation rates in the two groups did not reach statistical significance.

For early ultrasound surveillance to improve AVF outcomes, two conditions must be met: that ultrasound can reliably identify those fistulas that are either not going to mature or will fail early; and that the salvage interventions triggered by the ultrasound findings make a lasting improvement in fistula patency. Here we report the findings of the SONAR study; a prospective multicentre study involving several hundred patients that assessed whether ultrasound surveillance could reliably identify those AVFs that would either not mature or fail early, and if so, whether, within the constraints of standard UK vascular access provision, formal RCT evaluation of early ultrasound-directed salvage intervention was feasible.

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Methods

A prospective multicentre observational cohort study of adult patients undergoing formation of arteriovenous fistula for haemodialysis was performed, according to the previously published protocol (17). Adults (aged 16 or over) with ESRD and due creation of an AVF (with a minimum venous diameter of 2mm at chosen site for fistula creation) were eligible for inclusion; those with known central venous stenosis or those unable to provide full informed consent were excluded. Standard wrist or elbow arteriovenous fistulas were performed under local, regional or general anaesthetic according to unit and individual surgeon preference. Participants underwent Doppler ultrasound of their AVF at weeks 2, 4 and 6 after its creation, with AVF flow (brachial artery blood flow), venous diameter, and resistance index recorded, performed by the trial vascular scientists at each centre, according to a standardised study protocol (supplementary methods), and with clinical teams blinded to the ultrasound findings, unless a scan was simultaneously requested on clinical grounds, or the scan confirmed thrombosis of the fistula. The primary outcome, fistula maturation, was assessed by ultrasound at week 10, according to established surrogate ultrasound parameters ((18) wrist fistula: representative venous diameter ≥ 4mm, with flow >400 mLs/min; elbow fistula: representative venous fistula diameter ≥ 5mm, with flow >500 mLs/min). Non-maturation of the AVF at 10 weeks was defined as: AVF occlusion/thrombosis or abandonment within the study period (76 days post AVF creation); or failure to achieve (either reported at the week 10 scan or imputed) maturation. The 10-week timepoint for assessment of fistula maturity was chosen to provide sufficient time to capture all fistulas that were likely to mature spontaneously, in recognition that fistula maturation continues beyond 6 weeks (19, 20).

Assuming that early ultrasound surveillance predicts failure in 25% of AVFs, a total of 347 AVFs were required to achieve precision of ±10% for an estimated 72% positive predictive value (PPV), allowing for 10% dropout.

Mixed multivariable logistic regression (binary-data population average model with exchangeable correlation structure) of the early ultrasound scan data was then used to build separate models for wrist and elbow AVFs that contained the minimum number of measurements required to predict AVF **non-maturation** by 10 weeks. The following candidate variables were considered for model inclusion: pre-operative vein diameter; quality of artery (healthy or mildly, moderately, severely diseased) at the time of surgery; quality of vein (healthy or diseased but distensible, or not distensible) at the time of surgery; clinical prediction of fistula maturity; average resistance index at scan time-point(s); representative venous diameter at scan time-point(s); average flow at scan time-point(s); patient sex; patient age; and diabetes. Cases with scan data missing from all time points or

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with fistula failure prior to the time point being considered in the model were excluded. A purposeful variable selection approach was followed as recommended by Hosmer *et al (21)*. Evidence of non-linearity in continuous variables was visually explored using univariable LOWESS smoothing and statistically assessed using quadratic and logarithmic univariable fractional polynomials. Receiver operating characteristic (ROC) curves were used to assist decisions regarding the cut-off value to classify a fistula as a failure and to determine when surgical or radiological intervention on the developing AVF could be considered. The PPV and negative predictive value (NPV; the probability of AVF maturation given that the model predicts maturation) were calculated alongside a 95% confidence interval (CI) for the chosen risk-score cut-off and these parameters, together with the number of patients who could benefit from a salvage intervention in a future RCT, informed the clinical selection of the optimum models. Diagnostic tests for model fit and influential observations analysis performed on the optimum models revealed good model fit. All statistical analyses were carried out using Base SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

The strategies adopted for dealing with missing data are listed in the supplementary methods.

Additional modelling was then performed on a subset (n=192) of the original SONAR cohort available for follow-up, to assess whether fistula failure at 6 and 12 months could be identified by analysis of early ultrasound characteristics. The primary outcome measure for the longer term follow-up was primary fistula patency at 6 months, defined as, 'the interval between access creation to the earliest of fistula thrombosis, abandonment (except abandonment because of steal), intervention on the fistula (to *re-establish or maintain* patency), or the time of measurement of patency'. Secondary outcome measures included assisted primary patency (the interval from access creation until access thrombosis or the time of measurement of patency, including any interventions to maintain patency) and secondary patency (the interval from access creation to time of measurement of patency or to abandonment of the fistula). Similar binary-data population-average modelling was performed as for predicting 10 week non-maturation, aiming to build parsimonious models that contained the minimum number of variables from one scan time-point (either at week 4 or week 6) to effectively predict primary fistula non-patency at six months.

This study is in accordance with the Declaration of Istanbul, the ethical standards of our institution, and the 1964 Declaration of Helsinki. Informed consent was obtained from all participants involved in the study. The study was approved by the Cambridgeshire and Hertfordshire Research Ethics Committee and by the Health Research Authority (REC 18/EE/0234) and assigned ISRCTN 36033877.

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Results

Study participants and AVF surgery outcomes

Between 1/9/2018 and 11/11/2019, of 682 approaches at 17 UK haemodialysis sites were done, resulting in 347 consents to participation in the SONAR study (corresponding to 332 different participants; Figure s1). The demographics of the enrolments are provided in Table 1, and in general, mirrored contemporaneous UK experience (9), with the majority elderly and male; over 40% were diabetic. At enrolment, 191 (55.0%) cases were pre-dialysis, and a further 8 (2.3%) had received a previous transplant that was now failing.

Of those enrolled, 333 AVF fistulas were created (on 318 different participants) (Table 2), with slightly more elbow (52.3%) than wrist fistulas fashioned; 240 (72.1%) had formal pre-operative venous and arterial ultrasound mapping prior to surgery. Participants underwent Doppler ultrasound of their AVF at weeks 2, 4 and 6 after its creation, and fistula maturation was assessed at week 10, according to accepted surrogate ultrasound parameters.

By week 10, 219 (65.8%) of the 333 AVFs had reached maturity, with 67.2% of elbow and 60.4% of wrist AVFs maturing (Table 3). Fifty-seven (17.1%) had failed (either thrombosed or had been abandoned), but with 37 of the failures (64.9%) occurring before the first scan at two weeks, and 40 in total (70.2%) by the second scan at 4 weeks (Table s1). A relatively small number of AVFs remained patent, but not mature, at week 10 (n=29 (8.7%)), and the outcome of the remainder (n=28, 8.4%) not known and not imputable, because of non-attendance for ultrasound scanning.

Univariate analysis was performed to identify patient and pre-operative anatomical factors associated with fistula non-maturation at week 10. Candidate factors included: pre-operative vein diameter; quality of artery at the time of surgery; quality of vein at the time of surgery; clinical prediction of fistula maturity; patient sex; patient age; and history of diabetes. Pre-operative vein diameter was excluded in the wrist model due to missing values. Out of those factors known at baseline, only sex was univariately significant at the 5% level, and for wrist fistulas only. For elbow fistulas, no baseline factor was significant at the 5% level; pre-operative vein diameter, identified previously as an important predictive factor in AVF maturation (22-24), was not statistically significant.

Early ultrasound surveillance

Analysis of the early ultrasound findings revealed that the increases in AVF blood flow and venous diameter that characterise AVF maturation occur surprisingly rapidly (Figures 1A-1D, Table s2). For example, by week 2, a median AVF blood flow of 770 mLs/min and a median venous diameter of 5.2

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mm were achieved, excluding those AVFs that had already thrombosed. Thus, of those with scan data at week 2, 61.5% of wrist, and 62.0% of elbow, AVFs had reached maturation (Figure 1E and 1F). The proportion of wrist and elbow AVFs that were mature at the subsequent week 4, 6 and 10 week scans remained relatively constant, because although AVF maturation did occur beyond week 2, small numbers of AVFs either regressed to an immature state or had thrombosed on subsequent scanning (Figures 1G and 1H). The proportion of AVFs that were immature gradually decreased at each subsequent scan, either because they had matured or because they had thrombosed or had been abandoned (Figures 1G & 1H).

As shown in Figures 1a – 1d, analysis of the early ultrasound data revealed marked differences in recorded fistula vein diameter and fistula blood flow in those AVFs that reached maturity by week 10, compared to those that remained immature. For example, in those AVFs that reached maturity by week 10, median blood flow through the AVF on the week two scan was 1135.5 and 691.0 mLs/min for elbow and wrist AVF, respectively, whereas corresponding figures for elbow and wrist AVFs that remained immature were 349 and 395.5 mLs/min. Scatter plot diagrams of average fistula flow against fistula vein diameter for the week 2, 4, and 6 scan data (Figures 2a to 2c), highlight the different patterns of fistula development in those that will mature by week 10 compared to those that remain immature.

Logistic regression modelling of non-maturation from early ultrasound characteristics

The above data suggest that the early scan data could be used to identify those AVFs that will not reach maturity by week 10. If so, this identification may improve overall AVF patency, because it informs early radiological or surgical interventions that more successfully salvage the at-risk AVF than if delayed until initiated upon clinical grounds. Logistic regression was therefore used to construct models that incorporated the minimal number of variables from the pre-operative clinical and anatomical details and from the early scan data (preferably from an ultrasound scan at only one time-point) to effectively predict fistula ***non-maturation*** at 10 weeks. Missing data were imputed where possible, as detailed in supplementary data.

The optimum models considered elbow and wrist AVFs separately, and could be constructed from week 4 scan data only – including data from the earlier or later scans did not improve performance (Table 4 and Figure 3). Thus, for elbow AVFs, an algorithm that included the week 4 average resistance index and fistula blood flow predicted non-maturation at week 10 in 27 cases, and correctly so in 18 of these (true positives), giving a positive predictive value of 66.7% (95% CI 48.9 –

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84.4). The equivalent model for wrist AVFs incorporated week 4 fistula venous diameter and fistula blood flow, and predicted fistula non-maturation in 33 cases, with 20 of these true positives (positive predictive value 60.6% (95% CI 43.9 – 77.3%)). Diagnostic tests for model fit confirmed that both models performed well, with area under the curve (AUC) values of at least 0.9 (Figure 3). Interestingly, although the focus was on identifying on early surveillance ultrasound those AVFs that were not going to mature, the negative predictive value – i.e. the identification of those fistulas that *were going* to be mature at week 10 – was extremely high for both models (95.4% (91.0 – 99.8) for wrist and 95.6% (91.8 – 99.4) for elbow). Figure 4 provides a summary of the modelling of the week 4 ultrasound data in predicting week 10 AVF status. The models performed very similarly when only reported data was considered and imputed outcome data excluded (not shown).

Cohort one year follow-up

The justification for early salvage intervention is not simply that it would improve 10 week maturation, but that this would translate to better longer term AVF patency. In this regard, it was notable that, of the 74 AVFs that were patent on the week 4 ultrasound scan but did not reach maturity, only 17 had thrombosed by the week 10 scan, raising the possibility that the remainder could still be successfully salvaged at a later stage without recourse to early ultrasound surveillance. The relationship between the early ultrasound findings and longer term AVF outcomes were therefore assessed on a subset (n=192) of the original SONAR cohort available for follow-up. Participants were not required to attend any additional hospital appointments and primary patency at 6 months was reported in 99.0% of followed-up cases. Primary AVF patency at 6 months for all fistulas was 76.6% (69.9 – 82.4) and was higher at 6 months for elbow AVF than for wrist AVF (83.0% (73.8 - 89.9) vs. 70.4% (60.3 - 79.2)). This partly reflects the higher rate of early failure already noted for wrist AVFs, but as shown in Figure 5, wrist AVF failure also occurred after week 10. Notably, of the 42 elbow and wrist AVFs patent, but still immature, at 10 weeks, the majority (29 (69.0%)) had failed by 6 months; only a relatively small number (13 (31.0%)) matured successfully beyond 10 weeks (Figure s2).

Surgical (n=23) or radiological (n=20) 'salvage' procedures were attempted on 43 occasions on 38 AVFs in the first year after transplantation to either maintain or restore fistula patency. These interventions were successful in 79.1% of the procedures, and the assisted primary and secondary patency rates at 6 months (80.7% & 83.3%) and 12 months (74.1% & 79.5%) were therefore notably higher than the primary patency rates (Figure 5). Only five of these interventions (11.6%) occurred within 10 weeks of fistula creation, and these early interventions were prompted by notification

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from the vascular scientists that the fistula had thrombosed; the clinical teams were otherwise blinded to the scan results.

Logistic regression modelling was then performed to assess whether early ultrasound surveillance could predict primary fistula failure at 6 months (Table 5). As with the modelling for 10 week non-maturation, optimum models could be developed using ultrasound data from a single week, but separate models for predicting non-patency at 6 months for wrists and elbow AVFs performed superiorly, and relied on a different week's scan data. Thus for elbow AVFs, an algorithm that included: pre-operative vein diameter; week 4 average resistance index and fistula blood flow predicted 6-month non-patency in 7 cases, and correctly so (true positives) in four of these, giving a positive predictive value of 57.1% (20.5 – 93.8). A similar model could be developed for wrist fistulas, based on the week 6 scan data, and incorporated: fistula venous diameter; fistula blood flow; and average resistance index, with an additional interaction between sex of the participant and fistula venous diameter. This predicted non patency in 11 cases, with 8 true-positives, giving a PPV of 72.7% (46.4 – 99.0). Both models performed moderately well (Figure 6). As with the modelling for maturation status at 10 weeks, the models for 6 month patency were remarkably effective at identifying those fistulas that would be patent, with ***negative*** predictive values of 88.2% (80.9 – 95.4) and 91.3% (84.7 – 98.0) for elbow and wrist fistula, respectively.

Transferability of selected models.

Given the likelihood that similar early ultrasound characteristics would predict 10 week non-maturation and longer term AVF failure, one would perhaps anticipate that the optimum models for predicting wrist and elbow AVF 10 week non-maturation would perform well when tested for their ability to predict 6 month primary failure, and vice versa. However, as detailed in Table 6, this is not the case; when the model for 10-week fistula maturation is applied to the one-year follow-up cohort to predict 6-month primary fistula failure, the PPV falls to 31.8% and 22.2% for wrist and elbow fistulas, respectively. Similarly, neither the 10-week maturation nor the 6-month patency models could reliably predict assisted primary failure at 6 months – those AVFs that fail even after salvage intervention (Table 6).

One possible explanation why the model for 6 month primary fistula failure performs so poorly at predicting assisted primary failure is that those AVFs identified at risk of primary failure have their patency prolonged by successful salvage intervention. In support, predictive modelling of the 6 week ultrasound data identified 11 out of 80 wrist AVFs at risk of primary failure at 6 months, and salvage interventions to maintain or restore patency were performed on 8 (72.7%) of these, whereas only 6 of the 69 fistulas (8.7%) predicted as patent at six months underwent interventions to maintain or

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restore patency (Fisher's exact test, $p < 0.0001$). Similarly, 3 of the 7 (42.8%) elbow AVFs identified on the modelling of the 4 week ultrasound data as at risk of primary failure at 6 months underwent an intervention, with only 11 of the 76 (14.5%) AVFs predicted as patent experiencing an intervention (Fisher's exact test, $p = 0.0896$). Thus it appears that even without knowing the early ultrasound findings (the clinical teams were blinded to this data), a similar cohort of at risk AVFs could be identified, and subject to successful salvage intervention, on the basis of the later clinical manifestations.

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Discussion

Despite current guidelines from the National Kidney Foundation recommending that there is insufficient evidence to support ultrasound surveillance of AVFs (25), many centres have established protocols for performing routine Doppler ultrasound of AVFs that have matured and are being used for dialysis. Pick-up rates for these studies are low, because once mature, AVFs have generally favourable long-term patency. In contrast, the high rates of early failure following AVF creation, with as many as a third failing to mature, suggest that ultrasound surveillance of newly-formed AVFs has the potential to improve AVF patency rates more profoundly. This depends, however, not only upon successful identification of those AVFs that are likely to either fail early or not mature, but also on whether this informs timely salvage interventions that ultimately improve AVF maturation and patency rates. Thus, the SONAR study was designed to assess firstly; how reliably early ultrasound could identify those nascent AVFs at risk of failure or non-maturation, and then secondly; the feasibility of performing a prospective RCT that evaluates whether early surveillance, by directing timely and effective salvage intervention, leads to sustained improvements in fistula patency. In this latter objective, our study differs from the limited number of previous early ultrasound mapping studies, which have generally considered pre-operative factors that predict maturation (26) or have focused on detailing the maturation process (20, 24, 27).

Although there is a correlation between early ultrasound findings and subsequent AVF maturation/ patency, we conclude that introduction of an early ultrasound surveillance program would, at best, make only minimal improvements in AVF maturation and patency rates, and furthermore, that impractically large numbers of participants would be required to assess this potential benefit by formal RCT. This conclusion is based on several factors. Firstly, the AVF 10-week maturation and 6-month primary patency rates achieved by the SONAR consortium (65.8% and 76.6%, respectively) were generally better than had been anticipated at initial study design. Additionally, a high proportion of those AVFs that failed to mature had suffered early thrombosis. By week 2, 37 (11.1%) of AVFs had already failed (Table s1), and their outcome is unlikely to be altered by a surveillance program, no matter how early its implementation. Indeed, the modelling identified the week 4 scan as the most predictive for fistula non-maturation at week 10, and of the 293 of the original 333 (88.0%) study fistulas that were still patent at 4 weeks, maturation rates of 74.7% (95% CI: 69.4 – 79.6) were achieved. Factoring in an overall sensitivity of 80.5% (postulated from our modelling exercises where all fistulas (elbows and wrists) were considered together) for identifying those AVFs that will not mature, week-4 ultrasound surveillance could therefore potentially prevent non-maturation in 17.8% of AVFs created, but only if every at-risk AVF identified could then be

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successfully salvaged either surgically or radiologically. Thus, in powering for a RCT with 1:1 randomisation to standard care or to the treatment arm (salvage intervention of the AVF based on results of a week 4 ultrasound scan), if one postulates a more conservative intervention effect of 8% (equating to an intervention success rate of 60%), then relative to an event rate in the control arm of 65%, 1720 participants would be required (allowing for drop-out). Of the 860 patients randomised to the treatment group, estimates based on our optimum wrist week 4 model (the most conservative of our models) indicate that surveillance would result in 184 salvage interventions, with 72 of these unnecessary (the fistula would have matured successfully if managed conservatively), and of the 112 true positives, 78 interventions would be successful at restoring or maintaining patency. This would improve maturation rates from the postulated 65% to 73%, with surveillance missing a further 22 fistulas that fail to mature. Intervention success rates of 50% would theoretically improve AVF maturation from 65% to 71.5% (56/860), and would require almost 2000 participants.

We therefore decided to examine whether early surveillance ultrasound could predict longer term outcomes (6 and 12 month AVF patency), with assisted primary patency as primary end-point. However, the ability of the early ultrasound to model 6-month primary fistula failure was, if anything, poorer than for predicting 10-week maturation status, with only the wrist model worthy of consideration. It is perhaps surprising that the optimum models for predicting 10-week maturation and 6-month patency were not interchangeable, given that similar ultrasound features are considered in both. This possibly reflects that a similar cohort of fistulas to those identified as at risk on the early surveillance ultrasound are subject to late salvage intervention. These interventions were presumably initiated because of concerns relating to fistula maturation and patency (clinical teams were routinely blinded to the early scan results), and were generally successful at maintaining or restoring patency. This raises doubts on the premise that, by avoiding thrombosis and loss of the draining fistula vein for further fistula creation, early identification and salvage of at-risk fistulas maximises fistula patency. Rather, our results highlight that an observant approach, with interventions guided by the later clinical findings, achieves very respectable patency rates.

Finally, although not the main focus of our study, this ability to use early ultrasound to identify, with a high degree of certainty, those fistulas that will reach maturity and be patent at 6 months, is not without clinical relevance. Vascular access surgery is generally a tertiary specialty, and an early ultrasound scan that provides strong reassurance of short- and medium-term fistula patency would potentially allow the patient to be discharged back to their referring centre at an earlier stage, thereby rationalising patient care while minimising costs and travel times.

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Disclosures

The authors have no interests to declare. None declared.

Data Sharing Statement

The datasets generated and analysed during the study will be available upon request from the corresponding author. Reasonable requests with an acceptable scientific case will be considered. Transfer of data will require a Data Transfer Agreement (DTA).

Supplementary Material

Supplementary information is available at KI Report's website

Supplementary Methods

Missing data
Doppler ultrasound protocol

Supplementary Tables

Table s1: Primary outcome following AVF creation, considered at each scan time-point

Table s2: Ultrasound scan data

Supplementary Figures

Figure s1: Study CONSORT diagram

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Figure s2: Fistula status at key study time-points

STROBE statement

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Tables

Table 1: Baseline characteristics of SONAR participants - stratified by fistula maturity

	No AVF created	Primary fistula maturity by week 10	Primary fistula non-maturity by week 10	Overall
Number of enrolments [1]	14 (4.0)	213 (61.4)	120 (34.6)	347
Age (years) [2]	62 (51-69)	66 (52-74)	62 (51.5-74.5)	65 (52-74)
Sex				
Female	3 (2.4)	67 (55.0)	52 (42.6)	122
Male	11 (4.9)	146 (64.9)	68 (30.2)	225
Cause of renal failure				
Glomerulonephritis	0 (0.0)	13 (59.1)	9 (40.9)	22
Polycystic	1 (5.3)	11 (57.9)	7 (36.8)	19
Hypertension	1 (2.5)	29 (72.5)	10 (25.0)	40
Diabetic	7 (6.5)	57 (52.8)	44 (40.7)	108
Renovascular disease	0 (0.0)	9 (69.2)	4 (30.8)	13
Unknown	1 (2.3)	29 (65.9)	14 (31.8)	44
Other	4 (4.0)	64 (64.0)	32 (32.0)	100
Hypertension				
No	3 (4.7)	39 (62.0)	21 (33.3)	63
Yes	11 (3.9)	174 (61.3)	99 (34.9)	284
Diabetes				
No	4 (2.0)	126 (64.0)	67 (34.0)	197
Yes - insulin dependent	7 (7.9)	48 (53.9)	34 (38.2)	89
Yes - non-insulin dependent	3 (4.9)	39 (63.9)	19 (31.1)	61
IHD/CVA/PVD [3]				
No	13 (5.0)	159 (61.4)	87 (33.6)	259
Yes	1 (1.1)	53 (60.9)	33 (37.9)	87
Dialysis status at enrolment				
Pre-dialysis	9 (4.7)	124 (64.9)	58 (30.4)	191
Haemodialysis	5 (3.5)	79 (56.0)	57 (40.4)	141

	No AVF created	Primary fistula maturity by week 10	Primary fistula non-maturity by week 10	Overall
Peritoneal	7 (2.0)	4 (57.1)	3 (42.9)	7
Failing transplant	8 (2.3)	6 (75.0)	2 (25.0)	8
Current vascular access for haemodialysis				
Fistula	0 (0.0)	0 (00.0)	3 (100.0)	3
Graft	0 (0.0)	0 (0.0)	0 (0.0)	0
Line	5 (3.6)	79 (57.2)	54 (39.1)	138
Number of previous fistulas				
0	10 (3.7)	177 (64.8)	86 (31.5)	273
1	3 (7.0)	24 (55.8)	16 (37.2)	43
2	1 (4.3)	9 (39.1)	13 (56.5)	23
>2	0 (0.0)	3 (37.5)	5 (62.5)	8
Number of patients re-entering the study [4]				
With AVF surgery	0	5	9	14
Without AVF surgery	0	0	0	0

[1] From 332 participants, reflecting re-entry into the study upon failure of first study AVF and creation of another.

[2] Data are median (IQR) for continuous variables and N (row %) for categorical variables.

[3] IHD/CVA/PVD – Ischaemic heart disease / Cerebrovascular accident, peripheral vascular disease.

[4] Of 332 participants enrolled, 318 had an AVF created. There were 333 AVFs created in total on these 318 participants; 318 first-time SONAR fistulas, 14 second-time and 1 third-time. There were 14 participants re-enrolled; 13 of them re-enrolled once, 1 of them twice, totalling 15 re-enrolments on 14 different participants; all 14 participants underwent AVF surgery.

Summary of missing data: Cause of renal failure and IHD/CVA/PVD are each missing for 1 observation.

Table 2: AVF surgery details of SONAR enrolments - stratified by fistula maturity [1]

	Primary fistula maturity by week 10	Primary fistula non-maturity by week 10	Overall
Number of fistula operations performed [2]	213 (64.0)	120 (36.0)	333
Pre-operative mapping USS performed			
No	56 (60.2)	37 (39.8)	93
Yes	157 (65.4)	83 (34.6)	240
Anaesthesia [3]			
Local anaesthesia	179 (63.0)	105 (37.0)	284
Regional block	26 (72.2)	10 (27.8)	36
General anaesthetic	7 (58.3)	5 (41.7)	12
Side and site of fistula			
Left Wrist	**74 (63.8)**	**42 (36.2)**	**116**
Left – Radiocephalic	74	41	115
Left – Ulnobasilic	0	1	1
Left Elbow	**94 (70.1)**	**40 (29.9)**	**134**
Left – Brachiocephalic	77	32	109
Left – Brachiobasilic	17	8	25
Right Wrist	**22 (51.2)**	**21 (48.8)**	**43**
Right - Radiocephalic	22	21	43
Right - Ulnobasilic	0	0	0
Right Elbow	**23 (57.5)**	**17 (42.5)**	**40**
Right - Brachiocephalic	20	13	33
Right - Brachiobasilic	3	4	7

[1] Data are N (row %).
[2] Number of enrolments that did not undergo surgery is 14.
[3] Anaesthesia for 1 enrolment was reported as 'Other – axillary nerve block and general anaesthetic'.

Table 3: Primary outcome by week 10 following AVF creation

	All fistulas[2]		Elbows		Wrists	
	n/N	%	n/N	%	n/N	%
Mature	219/333	65.8%	117/174	67.2%	96/159	60.4%
Patent but non-mature	29/333	8.7%	19/174	10.9%	16/159	10.1%
Failed[1]	57/333	17.1%	18/174	10.3%	39/159	24.5%
Unknown	28/333	8.4%	20/174	11.5%	8/159	5.0%

[1] Failed means the fistula occluded/thrombosed or the fistula was abandoned due to failure to mature or due to thrombosis/occlusion.

[2] 'All fistula' criteria for maturity; representative venous diameter ≥4mm and average volume flow >400 mls/min.

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Table 4: Optimum models for predicting primary fistula non-maturation by week 10.

Week 4 factors included in model *	**Elbow (n =140)** ***odds ratio (95% CI)***	**Wrist (n = 120)** ***odds ratio (95% CI)***
Average resistance index (0.1 unit change from mean)	5.9 (2.6 – 13.3) **$p < 0.0001$**	NS
Average volume flow (100 unit change from mean)	0.8 (0.6 -1.0) **$p = 0.0224$**	2.2 (1.2 – 4.0) **$p = 0.0080$**
Representative venous diameter (1 unit change from mean)	NS	0.5 (0.3 – 0.7) **$p = 0.0006$**
Log of average volume flow at week 4 scan (1 unit change from mean)	NS	<0.001 (<0.001 – 0.019) **$p = 0.0005$**
Model performance		
Area under the curve value	0.92	0.90
Threshold *(Youden index)*	0.27	0.17
PPV for threshold (95% CI)	66.7% (48.9 – 84.4)	60.6% (43.9 – 77.3)
NPV for threshold (95% CI)	95.6% (91.8 – 99.4)	95.4% (91.0 – 99.8)
Number of predicted failures vs. actual failures	27 vs. 23	33 v. 24
Number of correctly predicted failures	18	20

* Variables considered for inclusion in the models were: pre-operative vein diameter[E,§]; quality of artery at the time of surgery[E,W]; quality of vein at the time of surgery[E,†]; clinical prediction of fistula maturity[E,W]; average resistance index at week 4[W]; representative venous diameter at week 4[E]; average flow at week 4; patient sex[E,W]; patient age[E,W] and diabetes[W,††]. In addition, the wrist model considered the interaction between representative venous diameter and average volume flow[†].

[E] Factor not included in the week 4 elbow model of primary fistula non-maturation by week 10. Non-statistically-significant (NS) factor, at the 5% significance level.

[W] Factor not included in the week 4 wrist model of primary fistula non-maturation by week 10. NS factor.

[§] Factor not considered in the candidate set of variables for the wrist model due to presence of missing data above the pre-determined cut-off of up to 30% data missing.

[†, ††] Statistically significant factor, at the 5% level in the multi-variable wrist[†] or elbow[††] model, but not included in the final model. Statistical significance was not the only criterion used to select variables for model building. Other criteria, such as the Hosmer, Lemeshow and Sturdivant (2013) delta-beta-hat-percent measure, as well as clinical relevance and parsimony, were also used.

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Table 5: Optimum models for predicting primary fistula non-patency at 6 months

Factors included in model [§]	**Elbow (n=83)** ***odds ratio (95% CI)***	**Wrist (n=80)** ***odds ratio (95% CI)***
Pre-operative vein diameter (1 unit change from mean)	1.57 (0.91 – 2.72) **$p = 0.1030$**	n/a
*Average resistance index * (0.1 unit change from mean)*	1.65 (0.61 – 4.46) **$p = 0.3146$**	2.59 (1.46 – 4.58) **$p = 0.0015$**
Average volume flow (100 unit change from mean)*	0.93 (0.83 – 1.05) **$p = 0.2471$**	1.13 (1.06 – 1.20) **$p = 0.0003$**
Sex ‡	NS	**$p = 0.0067$**
*Representative venous diameter *, ‡*	NS	***$p < 0.0001$***
*Interaction between sex and representative venous diameter **	n/a	**$p = 0.0003$**
1 unit change of representative diameter from mean for males		0.71 (0.53 – 0.95)
1 unit change of representative diameter from mean for females		0.09 (0.03 – 0.26)
Model performance		
Area under the curve value	0.71	0.81
Threshold *(Youden index)*	0.37	0.32
PPV for threshold (95% CI)	57.1% (20.5 – 93.8)	72.7% (46.4 – 99.0)
NPV for threshold (95% CI)	88.2% (80.9 – 95.4)	91.3% (84.7 – 98.0)
Number of predicted failures vs. actual failures	7 vs 13	11 vs 14
Number of correctly predicted failures [§§]	4	8

[§] Variables considered for inclusion in the models were: pre-operative vein diameter[+]; quality of artery at the time of surgery[E,W]; quality of vein at the time of surgery[E,W]; clinical prediction of fistula maturity[E,W]; average resistance index at scan timepoint[*]; representative venous diameter at scan timepoint[*,E]; average flow at scan timepoint[*]; patient sex[E]; patient age[E,W] and diabetes[E,W]. A significant p-value was not the only criterion used to select variables for model building. Other criteria, such as the Hosmer, Lemeshow and Sturdivant (2013) delta-beta-hat-percent measure, as well as clinical relevance, were also used.

* Week 4 scan data for elbow; week 6 scan data for wrist.

‡ Main effects odds ratio is not presented for the wrist model due this factor's involvement in an interaction term.

§§ Failure is defined as abandonment due to failure to mature or due to thrombosis/occlusion, or had an intervention following a thrombosis/occlusion or failure to mature/provide adequate access.

[E] Factor not included in the week 4 elbow model of primary fistula non-patency by month 6. Non-statistically-significant (NS) factor, at the 5% significance level.

[W] Factor not included in the week 6 wrist model of primary fistula non-patency by month 6. NS factor.

[+] Factor not considered in the candidate set of variables for the wrist model due to presence of missing data above the pre-determined cut-off of up to 30% data missing.

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Table 6: Validation of optimum SONAR and SONAR 12M models against primary fistula failure and assisted primary fistula failure at 6 months

	SONAR models	SONAR-12M models
Against primary fistula failure at 6 months		
PPV for optimum wrist model (95% CI)	31.8% (18.1 – 45.6)	72.7% (46.4 – 99.0)
NPV for optimum wrist model (95% CI)	94.7% (87.6 – 100.0)	91.3% (84.7 – 98.0)
PPV for optimum elbow model (95% CI)	22.2% (6.5 – 37.9)	57.1% (20.5 – 93.8)
NPV for optimum elbow model (95% CI)	87.5% (78.8 – 96.2)	88.2% (80.9 – 95.4)
Against assisted primary fistula failure at 6 months		
PPV for optimum wrist model (95% CI)	31.6% (16.8 – 46.4)	29.3% (15.3 – 43.2)
NPV for optimum wrist model (95% CI)	95.5% (89.3 – 100.0)	100.0% (100.0 – 100.0)
PPV for optimum elbow model (95% CI)	14.3% (1.3 – 27.3)	17.9% (3.7 – 32.0)
NPV for optimum elbow model (95% CI)	94.5% (88.5 – 100.0)	96.4% (91.4 – 100.0)

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Figure Legends

Figure 1 legend:

Representative fistula venous diameter **(a)** & **(b)** and fistula volume flow rate **(c)** & **(d)** for elbow (a & c) and wrist (b & d) according to maturation status at week 10. Box and whisker plot shows minimum value (after excluding outliers), 25th centile, median, 75th centile and maximum value (after excluding outliers) without imputation of primary outcome. Fistulas that failed before week 10 (thrombosis or abandonment after a failure) were excluded from the analysis.

Stacked 100% bar charts showing the proportion of **(e)** elbow and **(f)** wrist fistulas, with the following outcomes at each of weeks 2, 4, 6 and 10: died; withdrawn; abandoned; thrombosed; mature by ultrasound parameters (at that scan), not mature by ultrasound parameters (at that scan), unknown (did not attend scan or where missing data from the scan prevented determination of maturity). **(g)** & **(h)**: as for (e) and (f) but for all fistulas, presented as numbers and including arrows depicting status at next scan of those fistulas mature **(g)** or immature **(h)** at previous scan.

Figure 2 Legend:

Scatter plot of representative venous diameter by average volume flow at 2, 4 and 6 weeks (figures a, b, and c, respectively) with different symbols for matured/not matured fistulas at week 10 (as per primary outcome with no imputation).

Figure 3 Legend:

Standard ROC curves for the optimum models established for predicting week 10 fistula non-maturation from week 4 ultrasound findings for **(a)** elbow, and **(b)** wrist fistulas, with 1-specificity (x-axis) plotted against sensitivity (y-axis), and each point on the graph generated by using a different threshold point. The optimal threshold point chosen in our study is shown in the plot (Youden index, symbol "Y"); the threshold value is the number on the far left to the "Y".

Figure 4: Summary of week 4 ultrasound modelling on identifying 10-week fistula status

Figure 5 Legend:

Kaplan Meier analysis of primary, assisted primary, and secondary patency rates to 12 months for **a)** elbow and **b)** wrist AVFs. Numbers in brackets represent 12 month (+ 95% confidence interval) patency rates.

Figure 6 Legend:

Standard ROC curve analysis for the optimum models established for predicting 6-month fistula non-patency from **a)** week 6 ultrasound findings for wrist and **b)** week 4 ultrasound findings for elbow fistula, with 1-specificity (x-axis) plotted against sensitivity (y-axis), and each point on the graph generated by using a different threshold point. The optimal threshold point chosen in our study is shown in the plot (Youden index, symbol "Y"); the threshold value is the number on the far left to the "Y".

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Appendices

Appendix 1: Sonar Trial Group

Anna Sidders, Cara Hudson, Claire Foley, Valerie Hopkins, Emma Laing, Chloe Fitzpatrick-Creamer, Helen Thomas, Alison Deary (NHS Blood and Transplant Clinical Trials Unit).

Gavin J Pettigrew, James Richards, Mohammed Hossain, Dominic Summers, Matthew Slater, Laura Scott, Regin Lagaac, Veena Surendrakumar, Tobi Ayorinde, Igor Chipurovski, Manikandan Kathirvel, Manoj Thialli, Subhankar Paul, Andrew Norton (Cambridge University Hospital).

Simon Knight, Klaus Bond, Elizabeth Hardy, Joanne Widdup, Rachael Potter, Elisabeth Pugh, Karen Parsons, Kathryn Lafferty, Madita Gavrila, Sheera Sutherland, Ria Rabara (Oxford University Hospitals NHS Foundation Trust).

Rajesh Sivaprakasam, Kate Crawford, Amy Bolsworth, Naavalah Ngwa-Ndifor, Laura Clementoni (Bart's Health NHS Trust).

Reza Motallebzadeh, Mohammad Ayaz Hossain, Matthew Bartlett, Rani Badhan, Fernando Yuenchang, Phil Gardiner, Natasha Irani (Royal Free London NHS Foundation Trust).

Zia Moinuddin, Helena Edlin, Anna Jerram, Jessica Lai, Joyce Banda, Janet Bendle (Manchester University NHS Foundation Trust).

Sam Turner, Maria Morgan, William Owen, Sue Dawson, Simon Daniel, Karen Allsop (North Bristol NHS Trust).

Andrew Tambyraja, Sarah-Jane Carmichael, Tom Eadie, Rona Lochiel, Midel Lena, Karen Gallagher (Royal Infirmary of Edinburgh, NHS Lothian).

Nicholas Barnett, Soundrie Padayachee, Philip Eldridge, May Rabuya, Naomi Hare (Guy's & St Thomas' NHS Foundation Trust).

Subash Somalanka, Jashree Patel, Abbas Ghazanfar, Judy van Selm, Caroline Bodneck, Martia Augustin, Kwame Ansu, Nalin Khosla, Kashif Burney, Karen Dear, Duminda Basnayake, Laijee Benny (Epsom and St Helier University Hospitals NHS Trust).

James Hunter, Carl Tiivas, Samantha Hyndman, Maria Truslove, Gail Evans, Kerry Read (University Hospital Coventry and Warwickshire NHS Trust).

Sam Dutta, Andrew Beech, Sarah Brand, Tara MacCormick-Swanson (Nottingham University Hospitals NHS Trust).

Sarah Lawman, Darren Cheal, Mel Smith, Kate Trivedi, Valentina Toska, Lorraine Shah-Goodwin (Brighton & Sussex University Hospitals NHS Trust).

Tracey Salter, Adnan Bajwa, John Kerr, Ana Fleet, Lianne Chapman, Sarah Gee, Thanuja Weerasinghe, Lisa Kavanagh, Louise Rowe-Leete (Frimley Health NHS Foundation Trust).

George Smith, Paris Cai, Judith Long, Tracey Rowe (Hull University Teaching Hospitals NHS Trust).

Mohammed Aslam, Jeremy Crane (Imperial College Healthcare NHS Trust).

Atul Bagul, Mary Quashie-Akponeware, Kate Waters, Alexandra Howson (University Hospitals of Leicester NHS Trust).

Neil Hoye, Alycon Walker (South Tees Hospitals NHS Foundation Trust)

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Appendix 2: Author Contributions

James Richards (Locum Consultant in NORS, HPB and Transplant Surgery) was involved in the conception and design of the study, patient recruitment and data acquisition, and drafting of the report.

Dominic Summers (Consultant Transplant and Vascular Access Surgeon) was involved in the conception and design of the study, data acquisition, and drafting of the report.

Anna Sidders (Trial Manager) was involved in the conception and design of the study and drafting of the report.

Elisa Allen (Trial Statistician) was involved in the conception and design of the study, analysis and interpretation of the data and drafting of the report.

Helen Thomas (Head of Clinical Trial Statistics) was involved in the conception and design of the study, analysis and interpretation of the data and drafting of the report.

Mohammed Ayaz Hossain (Consultant Transplant Surgeon) was involved in the conception and design of the study, data acquisition, and drafting of the report.

Subhankar Paul (Senior Clinical Fellow in Transplant Surgery and Organ Retrieval) was involved in the conception and design of the study, data acquisition, and drafting of the report.

Matthew Slater (Vascular Scientist) was involved in the conception and design of the study, ultrasound data acquisition and drafting of the report.

Matthew Bartlett (Vascular Scientist) was involved in the conception and design of the study, ultrasound data acquisition and drafting of the report.

Regin Lagaac (Renal and Vascular Access Nurse) was involved in the conception and design of the study, data acquisition, and drafting of the report.

Emma Laing (Clinical Operations Manager) was involved in the conception and design of the study and drafting of the report.

Valerie Hopkins (Clinical Trial Coordinator) was involved in the conception and design of the study and drafting of the report.

Chloe Fitzpatrick-Creamer (Clinical Trial Administrator) was involved in the conception and design of the study and drafting of the report.

Cara Hudson (Trial Statistician) was involved in the conception and design of the study, analysis and interpretation of the data and drafting of the report.

Joseph Parsons (Trial Statistician) performed statistical analysis and interpretation of the data and drafting of the report.

Sam Turner (Consultant Renal Transplant and Vascular Access Surgeon) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting the of report.

Andrew Tambyraja (Consultant Vascular Surgeon) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Subash Somalanka (Consultant Nephrologist) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

James Hunter (Consultant Renal Transplant and Vascular Access Surgeon) is a Grant Co-applicant and Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Sam Dutta (Consultant Transplant and General Surgeon) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

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Neil Hoye (Consultant Nephrologist) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Sarah Lawman (Consultant Nephrologist) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Tracey Salter (Consultant Nephrologist) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Mohammed Aslam (Clinical Vascular Scientist) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Atul Bagul (Consultant Transplant and Endocrine Surgeon) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Rajesh Sivaprakasam (Consultant Transplant Surgeon) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

George Smith (Honorary Consultant Vascular Surgeon) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Zia Moinuddin (Consultant Transplant Surgeon) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Simon Knight (Honorary Consultant Transplant and Vascular Access Surgeon) is a Grant Co-applicant and Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Nicholas Barnett (Consultant Transplant and Vascular Access Surgeon) is a Grant Co-applicant and Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Reza Motallebzadeh (Consultant Renal Transplant Surgeon) is a Grant Co-applicant and Principal Investigator involved in the conception and design of the study, data acquisition, and drafting of the report.

Gavin J Pettigrew (Professor of Clinical and Experimental Transplantation) is the Grant Lead Applicant and Chief Investigator responsible for the conception and design of the study, data acquisition, the analysis and interpretation of the data and writing the report.

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Title Page

Title:

Early ultrasound surveillance of newly-created haemodialysis arteriovenous fistula

Authors

James Richards [1,2,3], Dominic Summers [1,2], Anna Sidders [4], Elisa Allen [4], Helen Thomas [4], Mohammed Ayaz Hossain [3], Subhankar Paul [1,2], Matthew Slater [1], Matthew Bartlett [3], Regin Lagaac [1], Emma Laing [4], Valerie Hopkins [4], Chloe Fitzpatrick-Creamer [4], Cara Hudson [4], Joseph Parsons [4], Sam Turner [5], Andrew Tambyraja [6], Subash Somalanka [7], James Hunter [8], Sam Dutta [9], Neil Hoye [10], Sarah Lawman [11], Tracey Salter [7,12], Mohammed Aslam [13] Atul Bagul [14], Rajesh Sivaprakasam [15], George Smith [16], Zia Moinuddin [17], Simon Knight [18], Nicholas Barnett [19], Reza Motallebzadeh [3], Gavin J Pettigrew *[1,2].

On behalf of the SONAR trial group [20].

[1] Addenbrooke's Hospital, Hill Road, Cambridge

[2] University of Cambridge, Hill Road, Cambridge

[3] Royal Free London NHS Foundation Trust

[4] NHS Blood and Transplant Clinical Trials Unit

[5] North Bristol NHS Trust

[6] Royal Infirmary of Edinburgh, NHS Lothian

[7] Epsom and St Helier University Hospitals NHS Trust

[8] University Hospital Coventry and Warwickshire NHS Trust

[9] Nottingham University Hospitals NHS Trust

[10] South Tees Hospitals NHS Foundation Trust

[11] Brighton & Sussex University Hospitals NHS Trust

[12] Frimley Health NHS Foundation Trust

[13] Imperial College Healthcare NHS Trust, London, UK

[14] University Hospitals of Leicester NHS Trust

[15] Bart's Health NHS Trust

[16] Hull University Teaching Hospitals NHS Trust

[17] Manchester University NHS Foundation Trust

[18] Oxford University Hospitals NHS Foundation Trust

[19] Guy's and St Thomas' NHS Foundation Trust

[20] See Appendix 1

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Corresponding author

Professor Gavin Pettigrew (gjp25@cam.ac.uk)

Department of Surgery, Box 202, Addenbrooke's Hospital CB2 0QQ

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Significance Statement

Approximately 30% of arteriovenous fistulas fail to mature. Ultrasound surveillance of developing fistulas may improve patency rates by directing successful salvage intervention, but has not been formally assessed. In the SONAR study, the ability of fortnightly ultrasound scanning to predict 10 week fistula maturation and 6 month patency was assessed on 333 newly-created fistulas. Early ultrasound identified those fistulas that would successfully mature and remain patent with over 90% predictive power, but was less effective at identifying those that would not mature or fail (~70% predictive power). Allied to the better than expected 6-month patency rates (76.5%), our results suggest that early ultrasound surveillance would be unlikely to improve fistula patency rates. Power calculations confirm that addressing this impact by randomised controlled trial is impractical.

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Abstract

Introduction:

We assess if ultrasound surveillance of newly-created arteriovenous fistulas (AVFs) can predict non-maturation sufficiently reliably to justify randomised controlled trial (RCT) evaluation of ultrasound-directed salvage intervention.

Methods:

Consenting adults underwent blinded fortnightly ultrasound scanning of their AVF after creation, with scan characteristics that predicted AVF non-maturation identified by logistic regression modelling.

Results:

Of 333 AVFs created, 65.8% matured by 10 weeks. Serial scanning revealed that maturation occurred rapidly, whereas consistently lower fistula flow rates and venous diameters were observed in those that did not mature. Wrist and elbow AVF non-maturation could be optimally modelled from the week four ultrasound parameters alone, but with only moderate positive predictive values (wrist, 60.6% (95% CI 43.9 – 77.3); elbow, 66.7% (48.9 - 84.4)). Moreover, 40 (70.2%) of the 57 AVFs that thrombosed by week 10 had already failed by the week 4 scan, thus limiting the potential of salvage procedures initiated by that scan's findings to alter overall maturation rates.
Modelling of the early ultrasound characteristics could also predict primary patency failure at 6 months, but that model performed poorly at predicting assisted primary failure (those AVFs that failed despite a salvage attempt), partly because patency of at-risk AVFs was maintained by successful salvage performed without recourse to the early scan data.

Conclusions:

Early ultrasound surveillance may predict fistula maturation, but is likely, at best, to result in only very modest improvements in fistula patency. Power calculations suggest that an impractically large number of participants (>1700) would be required for formal RCT evaluation.

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Introduction

For most individuals with end-stage renal disease (ESRD), arteriovenous fistulas (AVFs) are the preferred modality for providing haemodialysis. Compared to dialysis via a central venous catheter (CVC), AVF use is associated with decreased hospitalisation from bloodstream infections (1-5), thereby offering substantial cost savings (6, 7), and a 40% reduction in mortality (8). Despite this, as many as two-thirds of those commencing haemodialysis in the UK do so via a CVC (9). This partly reflects that, once created, AVFs must 'mature' over several weeks before they can be used for dialysis, with approximately 30% of fistulas failing to do so (10-15). These failures necessitate either salvage interventions or creation of a new fistula, thus potentially prolonging the requirement for dialysis via a CVC. Maturation failure and early thrombosis may, moreover, limit options for future AVF creation, by precluding re-use of the entire draining fistula vein.

AVF maturation is characterised by massive increases in blood flow through the AVF and marked expansion in the fistula vein diameter, with compensatory thickening or 'arterialisation' of the vein wall. Doppler ultrasound surveillance of AVFs immediately after their creation may therefore identify early flow characteristics or anatomical features (such as the development of juxta-anastomotic ('swing-segment') stenosis (16)), that predict subsequent maturation failure. By providing an opportunity for successful radiological or surgical salvage, potentially before terminal thrombosis of the AVF, such early identification may improve overall AVF patency and lessen the requirement for dialysis via a CVC. This, however, remains largely untested. One randomised controlled trial (RCT) (13), has evaluated routine early ultrasound and reported a 13.6% fistula failure in the surveillance group, compared to 25.4% in the control group (ultrasound performed selectively, according to clinical indication), but the study was powered for a relatively large (20%) effect size, and the difference in maturation rates in the two groups did not reach statistical significance.

For early ultrasound surveillance to improve AVF outcomes, two conditions must be met: that ultrasound can reliably identify those fistulas that are either not going to mature or will fail early; and that the salvage interventions triggered by the ultrasound findings make a lasting improvement in fistula patency. Here we report the findings of the SONAR study; a prospective multicentre study involving several hundred patients that assessed whether ultrasound surveillance could reliably identify those AVFs that would either not mature or fail early, and if so, whether, within the constraints of standard UK vascular access provision, formal RCT evaluation of early ultrasound-directed salvage intervention was feasible.

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Methods

A prospective multicentre observational cohort study of adult patients undergoing formation of arteriovenous fistula for haemodialysis was performed, according to the previously published protocol (17). Adults (aged 16 or over) with ESRD and due creation of an AVF (with a minimum venous diameter of 2mm at chosen site for fistula creation) were eligible for inclusion; those with known central venous stenosis or those unable to provide full informed consent were excluded. Standard wrist or elbow arteriovenous fistulas were performed under local, regional or general anaesthetic according to unit and individual surgeon preference. Participants underwent Doppler ultrasound of their AVF at weeks 2, 4 and 6 after its creation, with AVF flow (brachial artery blood flow), venous diameter, and resistance index recorded, performed by the trial vascular scientists at each centre, according to a standardised study protocol (supplementary methods), and with clinical teams blinded to the ultrasound findings, unless a scan was simultaneously requested on clinical grounds, or the scan confirmed thrombosis of the fistula. The primary outcome, fistula maturation, was assessed by ultrasound at week 10, according to established surrogate ultrasound parameters ((18) wrist fistula: representative venous diameter ≥ 4mm, with flow >400 mLs/min; elbow fistula: representative venous fistula diameter ≥ 5mm, with flow >500 mLs/min). Non-maturation of the AVF at 10 weeks was defined as: AVF occlusion/thrombosis or abandonment within the study period (76 days post AVF creation); or failure to achieve (either reported at the week 10 scan or imputed) maturation. The 10-week timepoint for assessment of fistula maturity was chosen to provide sufficient time to capture all fistulas that were likely to mature spontaneously, in recognition that fistula maturation continues beyond 6 weeks (19, 20).

Assuming that early ultrasound surveillance predicts failure in 25% of AVFs, a total of 347 AVFs were required to achieve precision of ±10% for an estimated 72% positive predictive value (PPV), allowing for 10% dropout.

Mixed multivariable logistic regression (binary-data population average model with exchangeable correlation structure) of the early ultrasound scan data was then used to build separate models for wrist and elbow AVFs that contained the minimum number of measurements required to predict AVF **non-maturation** by 10 weeks. The following candidate variables were considered for model inclusion: pre-operative vein diameter; quality of artery (healthy or mildly, moderately, severely diseased) at the time of surgery; quality of vein (healthy or diseased but distensible, or not distensible) at the time of surgery; clinical prediction of fistula maturity; average resistance index at scan time-point(s); representative venous diameter at scan time-point(s); average flow at scan time-point(s); patient sex; patient age; and diabetes. Cases with scan data missing from all time points or

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with fistula failure prior to the time point being considered in the model were excluded. A purposeful variable selection approach was followed as recommended by Hosmer *et al (21)*. Evidence of non-linearity in continuous variables was visually explored using univariable LOWESS smoothing and statistically assessed using quadratic and logarithmic univariable fractional polynomials. Receiver operating characteristic (ROC) curves were used to assist decisions regarding the cut-off value to classify a fistula as a failure and to determine when surgical or radiological intervention on the developing AVF could be considered. The PPV and negative predictive value (NPV; the probability of AVF maturation given that the model predicts maturation) were calculated alongside a 95% confidence interval (CI) for the chosen risk-score cut-off and these parameters, together with the number of patients who could benefit from a salvage intervention in a future RCT, informed the clinical selection of the optimum models. Diagnostic tests for model fit and influential observations analysis performed on the optimum models revealed good model fit. All statistical analyses were carried out using Base SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

The strategies adopted for dealing with missing data are listed in the supplementary methods.

Additional modelling was then performed on a subset (n=192) of the original SONAR cohort available for follow-up, to assess whether fistula failure at 6 and 12 months could be identified by analysis of early ultrasound characteristics. The primary outcome measure for the longer term follow-up was primary fistula patency at 6 months, defined as, 'the interval between access creation to the earliest of fistula thrombosis, abandonment (except abandonment because of steal), intervention on the fistula (to *re-establish or maintain* patency), or the time of measurement of patency'. Secondary outcome measures included assisted primary patency (the interval from access creation until access thrombosis or the time of measurement of patency, including any interventions to maintain patency) and secondary patency (the interval from access creation to time of measurement of patency or to abandonment of the fistula). Similar binary-data population-average modelling was performed as for predicting 10 week non-maturation, aiming to build parsimonious models that contained the minimum number of variables from one scan time-point (either at week 4 or week 6) to effectively predict primary fistula non-patency at six months.

This study is in accordance with the Declaration of Istanbul, the ethical standards of our institution, and the 1964 Declaration of Helsinki. Informed consent was obtained from all participants involved in the study. The study was approved by the Cambridgeshire and Hertfordshire Research Ethics Committee and by the Health Research Authority (REC 18/EE/0234) and assigned ISRCTN 36033877.

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Results

Study participants and AVF surgery outcomes

Between 1/9/2018 and 11/11/2019, of 682 approaches at 17 UK haemodialysis sites were done, resulting in 347 consents to participation in the SONAR study (corresponding to 332 different participants; Figure s1). The demographics of the enrolments are provided in Table 1, and in general, mirrored contemporaneous UK experience (9), with the majority elderly and male; over 40% were diabetic. At enrolment, 191 (55.0%) cases were pre-dialysis, and a further 8 (2.3%) had received a previous transplant that was now failing.

Of those enrolled, 333 AVF fistulas were created (on 318 different participants) (Table 2), with slightly more elbow (52.3%) than wrist fistulas fashioned; 240 (72.1%) had formal pre-operative venous and arterial ultrasound mapping prior to surgery. Participants underwent Doppler ultrasound of their AVF at weeks 2, 4 and 6 after its creation, and fistula maturation was assessed at week 10, according to accepted surrogate ultrasound parameters.

By week 10, 219 (65.8%) of the 333 AVFs had reached maturity, with 67.2% of elbow and 60.4% of wrist AVFs maturing (Table 3). Fifty-seven (17.1%) had failed (either thrombosed or had been abandoned), but with 37 of the failures (64.9%) occurring before the first scan at two weeks, and 40 in total (70.2%) by the second scan at 4 weeks (Table s1). A relatively small number of AVFs remained patent, but not mature, at week 10 (n=29 (8.7%)), and the outcome of the remainder (n=28, 8.4%) not known and not imputable, because of non-attendance for ultrasound scanning.

Univariate analysis was performed to identify patient and pre-operative anatomical factors associated with fistula non-maturation at week 10. Candidate factors included: pre-operative vein diameter; quality of artery at the time of surgery; quality of vein at the time of surgery; clinical prediction of fistula maturity; patient sex; patient age; and history of diabetes. Pre-operative vein diameter was excluded in the wrist model due to missing values. Out of those factors known at baseline, only sex was univariately significant at the 5% level, and for wrist fistulas only. For elbow fistulas, no baseline factor was significant at the 5% level; pre-operative vein diameter, identified previously as an important predictive factor in AVF maturation (22-24), was not statistically significant.

Early ultrasound surveillance

Analysis of the early ultrasound findings revealed that the increases in AVF blood flow and venous diameter that characterise AVF maturation occur surprisingly rapidly (Figures 1A-1D, Table s2). For example, by week 2, a median AVF blood flow of 770 mLs/min and a median venous diameter of 5.2

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mm were achieved, excluding those AVFs that had already thrombosed. Thus, of those with scan data at week 2, 61.5% of wrist, and 62.0% of elbow, AVFs had reached maturation (Figure 1E and 1F). The proportion of wrist and elbow AVFs that were mature at the subsequent week 4, 6 and 10 week scans remained relatively constant, because although AVF maturation did occur beyond week 2, small numbers of AVFs either regressed to an immature state or had thrombosed on subsequent scanning (Figures 1G and 1H). The proportion of AVFs that were immature gradually decreased at each subsequent scan, either because they had matured or because they had thrombosed or had been abandoned (Figures 1G & 1H).

As shown in Figures 1a – 1d, analysis of the early ultrasound data revealed marked differences in recorded fistula vein diameter and fistula blood flow in those AVFs that reached maturity by week 10, compared to those that remained immature. For example, in those AVFs that reached maturity by week 10, median blood flow through the AVF on the week two scan was 1135.5 and 691.0 mLs/min for elbow and wrist AVF, respectively, whereas corresponding figures for elbow and wrist AVFs that remained immature were 349 and 395.5 mLs/min. Scatter plot diagrams of average fistula flow against fistula vein diameter for the week 2, 4, and 6 scan data (Figures 2a to 2c), highlight the different patterns of fistula development in those that will mature by week 10 compared to those that remain immature.

Logistic regression modelling of non-maturation from early ultrasound characteristics

The above data suggest that the early scan data could be used to identify those AVFs that will not reach maturity by week 10. If so, this identification may improve overall AVF patency, because it informs early radiological or surgical interventions that more successfully salvage the at-risk AVF than if delayed until initiated upon clinical grounds. Logistic regression was therefore used to construct models that incorporated the minimal number of variables from the pre-operative clinical and anatomical details and from the early scan data (preferably from an ultrasound scan at only one time-point) to effectively predict fistula ***non-maturation*** at 10 weeks. Missing data were imputed where possible, as detailed in supplementary data.

The optimum models considered elbow and wrist AVFs separately, and could be constructed from week 4 scan data only – including data from the earlier or later scans did not improve performance (Table 4 and Figure 3). Thus, for elbow AVFs, an algorithm that included the week 4 average resistance index and fistula blood flow predicted non-maturation at week 10 in 27 cases, and correctly so in 18 of these (true positives), giving a positive predictive value of 66.7% (95% CI 48.9 –

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84.4). The equivalent model for wrist AVFs incorporated week 4 fistula venous diameter and fistula blood flow, and predicted fistula non-maturation in 33 cases, with 20 of these true positives (positive predictive value 60.6% (95% CI 43.9 – 77.3%)). Diagnostic tests for model fit confirmed that both models performed well, with area under the curve (AUC) values of at least 0.9 (Figure 3). Interestingly, although the focus was on identifying on early surveillance ultrasound those AVFs that were not going to mature, the negative predictive value – i.e. the identification of those fistulas that *were going* to be mature at week 10 – was extremely high for both models (95.4% (91.0 – 99.8) for wrist and 95.6% (91.8 – 99.4) for elbow). Figure 4 provides a summary of the modelling of the week 4 ultrasound data in predicting week 10 AVF status. The models performed very similarly when only reported data was considered and imputed outcome data excluded (not shown).

Cohort one year follow-up

The justification for early salvage intervention is not simply that it would improve 10 week maturation, but that this would translate to better longer term AVF patency. In this regard, it was notable that, of the 74 AVFs that were patent on the week 4 ultrasound scan but did not reach maturity, only 17 had thrombosed by the week 10 scan, raising the possibility that the remainder could still be successfully salvaged at a later stage without recourse to early ultrasound surveillance. The relationship between the early ultrasound findings and longer term AVF outcomes were therefore assessed on a subset (n=192) of the original SONAR cohort available for follow-up. Participants were not required to attend any additional hospital appointments and primary patency at 6 months was reported in 99.0% of followed-up cases. Primary AVF patency at 6 months for all fistulas was 76.6% (69.9 – 82.4) and was higher at 6 months for elbow AVF than for wrist AVF (83.0% (73.8 - 89.9) vs. 70.4% (60.3 - 79.2)). This partly reflects the higher rate of early failure already noted for wrist AVFs, but as shown in Figure 5, wrist AVF failure also occurred after week 10. Notably, of the 42 elbow and wrist AVFs patent, but still immature, at 10 weeks, the majority (29 (69.0%)) had failed by 6 months; only a relatively small number (13 (31.0%)) matured successfully beyond 10 weeks (Figure s2).

Surgical (n=23) or radiological (n=20) 'salvage' procedures were attempted on 43 occasions on 38 AVFs in the first year after transplantation to either maintain or restore fistula patency. These interventions were successful in 79.1% of the procedures, and the assisted primary and secondary patency rates at 6 months (80.7% & 83.3%) and 12 months (74.1% & 79.5%) were therefore notably higher than the primary patency rates (Figure 5). Only five of these interventions (11.6%) occurred within 10 weeks of fistula creation, and these early interventions were prompted by notification

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from the vascular scientists that the fistula had thrombosed; the clinical teams were otherwise blinded to the scan results.

Logistic regression modelling was then performed to assess whether early ultrasound surveillance could predict primary fistula failure at 6 months (Table 5). As with the modelling for 10 week non-maturation, optimum models could be developed using ultrasound data from a single week, but separate models for predicting non-patency at 6 months for wrists and elbow AVFs performed superiorly, and relied on a different week's scan data. Thus for elbow AVFs, an algorithm that included: pre-operative vein diameter; week 4 average resistance index and fistula blood flow predicted 6-month non-patency in 7 cases, and correctly so (true positives) in four of these, giving a positive predictive value of 57.1% (20.5 – 93.8). A similar model could be developed for wrist fistulas, based on the week 6 scan data, and incorporated: fistula venous diameter; fistula blood flow; and average resistance index, with an additional interaction between sex of the participant and fistula venous diameter. This predicted non patency in 11 cases, with 8 true-positives, giving a PPV of 72.7% (46.4 – 99.0). Both models performed moderately well (Figure 6). As with the modelling for maturation status at 10 weeks, the models for 6 month patency were remarkably effective at identifying those fistulas that would be patent, with ***negative*** predictive values of 88.2% (80.9 – 95.4) and 91.3% (84.7 – 98.0) for elbow and wrist fistula, respectively.

Transferability of selected models.

Given the likelihood that similar early ultrasound characteristics would predict 10 week non-maturation and longer term AVF failure, one would perhaps anticipate that the optimum models for predicting wrist and elbow AVF 10 week non-maturation would perform well when tested for their ability to predict 6 month primary failure, and vice versa. However, as detailed in Table 6, this is not the case; when the model for 10-week fistula maturation is applied to the one-year follow-up cohort to predict 6-month primary fistula failure, the PPV falls to 31.8% and 22.2% for wrist and elbow fistulas, respectively. Similarly, neither the 10-week maturation nor the 6-month patency models could reliably predict assisted primary failure at 6 months – those AVFs that fail even after salvage intervention (Table 6).

One possible explanation why the model for 6 month primary fistula failure performs so poorly at predicting assisted primary failure is that those AVFs identified at risk of primary failure have their patency prolonged by successful salvage intervention. In support, predictive modelling of the 6 week ultrasound data identified 11 out of 80 wrist AVFs at risk of primary failure at 6 months, and salvage interventions to maintain or restore patency were performed on 8 (72.7%) of these, whereas only 6 of the 69 fistulas (8.7%) predicted as patent at six months underwent interventions to maintain or

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restore patency (Fisher's exact test, $p < 0.0001$). Similarly, 3 of the 7 (42.8%) elbow AVFs identified on the modelling of the 4 week ultrasound data as at risk of primary failure at 6 months underwent an intervention, with only 11 of the 76 (14.5%) AVFs predicted as patent experiencing an intervention (Fisher's exact test, $p = 0.0896$). Thus it appears that even without knowing the early ultrasound findings (the clinical teams were blinded to this data), a similar cohort of at risk AVFs could be identified, and subject to successful salvage intervention, on the basis of the later clinical manifestations.

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Discussion

Despite current guidelines from the National Kidney Foundation recommending that there is insufficient evidence to support ultrasound surveillance of AVFs (25), many centres have established protocols for performing routine Doppler ultrasound of AVFs that have matured and are being used for dialysis. Pick-up rates for these studies are low, because once mature, AVFs have generally favourable long-term patency. In contrast, the high rates of early failure following AVF creation, with as many as a third failing to mature, suggest that ultrasound surveillance of newly-formed AVFs has the potential to improve AVF patency rates more profoundly. This depends, however, not only upon successful identification of those AVFs that are likely to either fail early or not mature, but also on whether this informs timely salvage interventions that ultimately improve AVF maturation and patency rates. Thus, the SONAR study was designed to assess firstly; how reliably early ultrasound could identify those nascent AVFs at risk of failure or non-maturation, and then secondly; the feasibility of performing a prospective RCT that evaluates whether early surveillance, by directing timely and effective salvage intervention, leads to sustained improvements in fistula patency. In this latter objective, our study differs from the limited number of previous early ultrasound mapping studies, which have generally considered pre-operative factors that predict maturation (26) or have focused on detailing the maturation process (20, 24, 27).

Although there is a correlation between early ultrasound findings and subsequent AVF maturation/ patency, we conclude that introduction of an early ultrasound surveillance program would, at best, make only minimal improvements in AVF maturation and patency rates, and furthermore, that impractically large numbers of participants would be required to assess this potential benefit by formal RCT. This conclusion is based on several factors. Firstly, the AVF 10-week maturation and 6-month primary patency rates achieved by the SONAR consortium (65.8% and 76.6%, respectively) were generally better than had been anticipated at initial study design. Additionally, a high proportion of those AVFs that failed to mature had suffered early thrombosis. By week 2, 37 (11.1%) of AVFs had already failed (Table s1), and their outcome is unlikely to be altered by a surveillance program, no matter how early its implementation. Indeed, the modelling identified the week 4 scan as the most predictive for fistula non-maturation at week 10, and of the 293 of the original 333 (88.0%) study fistulas that were still patent at 4 weeks, maturation rates of 74.7% (95% CI: 69.4 – 79.6) were achieved. Factoring in an overall sensitivity of 80.5% (postulated from our modelling exercises where all fistulas (elbows and wrists) were considered together) for identifying those AVFs that will not mature, week-4 ultrasound surveillance could therefore potentially prevent non-maturation in 17.8% of AVFs created, but only if every at-risk AVF identified could then be

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successfully salvaged either surgically or radiologically. Thus, in powering for a RCT with 1:1 randomisation to standard care or to the treatment arm (salvage intervention of the AVF based on results of a week 4 ultrasound scan), if one postulates a more conservative intervention effect of 8% (equating to an intervention success rate of 60%), then relative to an event rate in the control arm of 65%, 1720 participants would be required (allowing for drop-out). Of the 860 patients randomised to the treatment group, estimates based on our optimum wrist week 4 model (the most conservative of our models) indicate that surveillance would result in 184 salvage interventions, with 72 of these unnecessary (the fistula would have matured successfully if managed conservatively), and of the 112 true positives, 78 interventions would be successful at restoring or maintaining patency. This would improve maturation rates from the postulated 65% to 73%, with surveillance missing a further 22 fistulas that fail to mature. Intervention success rates of 50% would theoretically improve AVF maturation from 65% to 71.5% (56/860), and would require almost 2000 participants.

We therefore decided to examine whether early surveillance ultrasound could predict longer term outcomes (6 and 12 month AVF patency), with assisted primary patency as primary end-point. However, the ability of the early ultrasound to model 6-month primary fistula failure was, if anything, poorer than for predicting 10-week maturation status, with only the wrist model worthy of consideration. It is perhaps surprising that the optimum models for predicting 10-week maturation and 6-month patency were not interchangeable, given that similar ultrasound features are considered in both. This possibly reflects that a similar cohort of fistulas to those identified as at risk on the early surveillance ultrasound are subject to late salvage intervention. These interventions were presumably initiated because of concerns relating to fistula maturation and patency (clinical teams were routinely blinded to the early scan results), and were generally successful at maintaining or restoring patency. This raises doubts on the premise that, by avoiding thrombosis and loss of the draining fistula vein for further fistula creation, early identification and salvage of at-risk fistulas maximises fistula patency. Rather, our results highlight that an observant approach, with interventions guided by the later clinical findings, achieves very respectable patency rates.

Finally, although not the main focus of our study, this ability to use early ultrasound to identify, with a high degree of certainty, those fistulas that will reach maturity and be patent at 6 months, is not without clinical relevance. Vascular access surgery is generally a tertiary specialty, and an early ultrasound scan that provides strong reassurance of short- and medium-term fistula patency would potentially allow the patient to be discharged back to their referring centre at an earlier stage, thereby rationalising patient care while minimising costs and travel times.

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Disclosures

The authors have no interests to declare. None declared.

Data Sharing Statement

The datasets generated and analysed during the study will be available upon request from the corresponding author. Reasonable requests with an acceptable scientific case will be considered. Transfer of data will require a Data Transfer Agreement (DTA).

Supplementary Material

Supplementary information is available at KI Report's website

Supplementary Methods

Missing data
Doppler ultrasound protocol

Supplementary Tables

Table s1: Primary outcome following AVF creation, considered at each scan time-point

Table s2: Ultrasound scan data

Supplementary Figures

Figure s1: Study CONSORT diagram

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Figure s2: Fistula status at key study time-points

STROBE statement

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Tables

Table 1: Baseline characteristics of SONAR participants - stratified by fistula maturity

	No AVF created	Primary fistula maturity by week 10	Primary fistula non-maturity by week 10	Overall
Number of enrolments [1]	14 (4.0)	213 (61.4)	120 (34.6)	347
Age (years) [2]	62 (51-69)	66 (52-74)	62 (51.5-74.5)	65 (52-74)
Sex				
Female	3 (2.4)	67 (55.0)	52 (42.6)	122
Male	11 (4.9)	146 (64.9)	68 (30.2)	225
Cause of renal failure				
Glomerulonephritis	0 (0.0)	13 (59.1)	9 (40.9)	22
Polycystic	1 (5.3)	11 (57.9)	7 (36.8)	19
Hypertension	1 (2.5)	29 (72.5)	10 (25.0)	40
Diabetic	7 (6.5)	57 (52.8)	44 (40.7)	108
Renovascular disease	0 (0.0)	9 (69.2)	4 (30.8)	13
Unknown	1 (2.3)	29 (65.9)	14 (31.8)	44
Other	4 (4.0)	64 (64.0)	32 (32.0)	100
Hypertension				
No	3 (4.7)	39 (62.0)	21 (33.3)	63
Yes	11 (3.9)	174 (61.3)	99 (34.9)	284
Diabetes				
No	4 (2.0)	126 (64.0)	67 (34.0)	197
Yes - insulin dependent	7 (7.9)	48 (53.9)	34 (38.2)	89
Yes - non-insulin dependent	3 (4.9)	39 (63.9)	19 (31.1)	61
IHD/CVA/PVD [3]				
No	13 (5.0)	159 (61.4)	87 (33.6)	259
Yes	1 (1.1)	53 (60.9)	33 (37.9)	87
Dialysis status at enrolment				
Pre-dialysis	9 (4.7)	124 (64.9)	58 (30.4)	191
Haemodialysis	5 (3.5)	79 (56.0)	57 (40.4)	141

	No AVF created	Primary fistula maturity by week 10	Primary fistula non-maturity by week 10	Overall
Peritoneal	7 (2.0)	4 (57.1)	3 (42.9)	7
Failing transplant	8 (2.3)	6 (75.0)	2 (25.0)	8
Current vascular access for haemodialysis				
Fistula	0 (0.0)	0 (00.0)	3 (100.0)	3
Graft	0 (0.0)	0 (0.0)	0 (0.0)	0
Line	5 (3.6)	79 (57.2)	54 (39.1)	138
Number of previous fistulas				
0	10 (3.7)	177 (64.8)	86 (31.5)	273
1	3 (7.0)	24 (55.8)	16 (37.2)	43
2	1 (4.3)	9 (39.1)	13 (56.5)	23
>2	0 (0.0)	3 (37.5)	5 (62.5)	8
Number of patients re-entering the study [4]				
With AVF surgery	0	5	9	14
Without AVF surgery	0	0	0	0

[1] From 332 participants, reflecting re-entry into the study upon failure of first study AVF and creation of another.

[2] Data are median (IQR) for continuous variables and N (row %) for categorical variables.

[3] IHD/CVA/PVD – Ischaemic heart disease / Cerebrovascular accident, peripheral vascular disease.

[4] Of 332 participants enrolled, 318 had an AVF created. There were 333 AVFs created in total on these 318 participants; 318 first-time SONAR fistulas, 14 second-time and 1 third-time. There were 14 participants re-enrolled; 13 of them re-enrolled once, 1 of them twice, totalling 15 re-enrolments on 14 different participants; all 14 participants underwent AVF surgery.

Summary of missing data: Cause of renal failure and IHD/CVA/PVD are each missing for 1 observation.

Table 2: AVF surgery details of SONAR enrolments - stratified by fistula maturity [1]

	Primary fistula maturity by week 10	Primary fistula non-maturity by week 10	Overall
Number of fistula operations performed [2]	213 (64.0)	120 (36.0)	333
Pre-operative mapping USS performed			
No	56 (60.2)	37 (39.8)	93
Yes	157 (65.4)	83 (34.6)	240
Anaesthesia [3]			
Local anaesthesia	179 (63.0)	105 (37.0)	284
Regional block	26 (72.2)	10 (27.8)	36
General anaesthetic	7 (58.3)	5 (41.7)	12
Side and site of fistula			
Left Wrist	**74 (63.8)**	**42 (36.2)**	**116**
Left – Radiocephalic	74	41	115
Left – Ulnobasilic	0	1	1
Left Elbow	**94 (70.1)**	**40 (29.9)**	**134**
Left – Brachiocephalic	77	32	109
Left – Brachiobasilic	17	8	25
Right Wrist	**22 (51.2)**	**21 (48.8)**	**43**
Right - Radiocephalic	22	21	43
Right - Ulnobasilic	0	0	0
Right Elbow	**23 (57.5)**	**17 (42.5)**	**40**
Right - Brachiocephalic	20	13	33
Right - Brachiobasilic	3	4	7

[1] Data are N (row %).
[2] Number of enrolments that did not undergo surgery is 14.
[3] Anaesthesia for 1 enrolment was reported as 'Other – axillary nerve block and general anaesthetic'.

Table 3: Primary outcome by week 10 following AVF creation

	All fistulas[2]		Elbows		Wrists	
	n/N	%	n/N	%	n/N	%
Mature	219/333	65.8%	117/174	67.2%	96/159	60.4%
Patent but non-mature	29/333	8.7%	19/174	10.9%	16/159	10.1%
Failed[1]	57/333	17.1%	18/174	10.3%	39/159	24.5%
Unknown	28/333	8.4%	20/174	11.5%	8/159	5.0%

[1] Failed means the fistula occluded/thrombosed or the fistula was abandoned due to failure to mature or due to thrombosis/occlusion.

[2] 'All fistula' criteria for maturity; representative venous diameter ≥4mm and average volume flow >400 mls/min.

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Table 4: Optimum models for predicting primary fistula non-maturation by week 10.

Week 4 factors included in model *	**Elbow (n =140)** ***odds ratio (95% CI)***	**Wrist (n = 120)** ***odds ratio (95% CI)***
Average resistance index (0.1 unit change from mean)	5.9 (2.6 – 13.3) **$p < 0.0001$**	NS
Average volume flow (100 unit change from mean)	0.8 (0.6 -1.0) **$p = 0.0224$**	2.2 (1.2 – 4.0) **$p = 0.0080$**
Representative venous diameter (1 unit change from mean)	NS	0.5 (0.3 – 0.7) **$p = 0.0006$**
Log of average volume flow at week 4 scan (1 unit change from mean)	NS	<0.001 (<0.001 – 0.019) **$p = 0.0005$**
Model performance		
Area under the curve value	0.92	0.90
Threshold *(Youden index)*	0.27	0.17
PPV for threshold (95% CI)	66.7% (48.9 – 84.4)	60.6% (43.9 – 77.3)
NPV for threshold (95% CI)	95.6% (91.8 – 99.4)	95.4% (91.0 – 99.8)
Number of predicted failures vs. actual failures	27 vs. 23	33 v. 24
Number of correctly predicted failures	18	20

* Variables considered for inclusion in the models were: pre-operative vein diameter[E,§]; quality of artery at the time of surgery[E,W]; quality of vein at the time of surgery[E,†]; clinical prediction of fistula maturity[E,W]; average resistance index at week 4[W]; representative venous diameter at week 4[E]; average flow at week 4; patient sex[E,W]; patient age[E,W] and diabetes[W,††]. In addition, the wrist model considered the interaction between representative venous diameter and average volume flow[†].

[E] Factor not included in the week 4 elbow model of primary fistula non-maturation by week 10. Non-statistically-significant (NS) factor, at the 5% significance level.

[W] Factor not included in the week 4 wrist model of primary fistula non-maturation by week 10. NS factor.

[§] Factor not considered in the candidate set of variables for the wrist model due to presence of missing data above the pre-determined cut-off of up to 30% data missing.

[†, ††] Statistically significant factor, at the 5% level in the multi-variable wrist[†] or elbow[††] model, but not included in the final model. Statistical significance was not the only criterion used to select variables for model building. Other criteria, such as the Hosmer, Lemeshow and Sturdivant (2013) delta-beta-hat-percent measure, as well as clinical relevance and parsimony, were also used.

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Table 5: Optimum models for predicting primary fistula non-patency at 6 months

Factors included in model §	Elbow (n=83) *odds ratio (95% CI)*	Wrist (n=80) *odds ratio (95% CI)*
Pre-operative vein diameter (1 unit change from mean)	1.57 (0.91 – 2.72) **$p = 0.1030$**	n/a
*Average resistance index * (0.1 unit change from mean)*	1.65 (0.61 – 4.46) **$p = 0.3146$**	2.59 (1.46 – 4.58) **$p = 0.0015$**
Average volume flow (100 unit change from mean)*	0.93 (0.83 – 1.05) **$p = 0.2471$**	1.13 (1.06 – 1.20) **$p = 0.0003$**
Sex ‡	NS	**$p = 0.0067$**
*Representative venous diameter *, ‡*	NS	***$p < 0.0001$***
*Interaction between sex and representative venous diameter **	n/a	**$p = 0.0003$**
1 unit change of representative diameter from mean for males		0.71 (0.53 – 0.95)
1 unit change of representative diameter from mean for females		0.09 (0.03 – 0.26)
Model performance		
Area under the curve value	0.71	0.81
Threshold *(Youden index)*	0.37	0.32
PPV for threshold (95% CI)	57.1% (20.5 – 93.8)	72.7% (46.4 – 99.0)
NPV for threshold (95% CI)	88.2% (80.9 – 95.4)	91.3% (84.7 – 98.0)
Number of predicted failures vs. actual failures	7 vs 13	11 vs 14
Number of correctly predicted failures §§	4	8

§ Variables considered for inclusion in the models were: pre-operative vein diameter+; quality of artery at the time of surgery[E,W]; quality of vein at the time of surgery[E,W]; clinical prediction of fistula maturity[E,W]; average resistance index at scan timepoint*; representative venous diameter at scan timepoint*,E; average flow at scan timepoint*; patient sex[E]; patient age[E,W] and diabetes[E,W]. A significant p-value was not the only criterion used to select variables for model building. Other criteria, such as the Hosmer, Lemeshow and Sturdivant (2013) delta-beta-hat-percent measure, as well as clinical relevance, were also used.

* Week 4 scan data for elbow; week 6 scan data for wrist.

‡ Main effects odds ratio is not presented for the wrist model due this factor's involvement in an interaction term.

§§ Failure is defined as abandonment due to failure to mature or due to thrombosis/occlusion, or had an intervention following a thrombosis/occlusion or failure to mature/provide adequate access.

[E] Factor not included in the week 4 elbow model of primary fistula non-patency by month 6. Non-statistically-significant (NS) factor, at the 5% significance level.

[W] Factor not included in the week 6 wrist model of primary fistula non-patency by month 6. NS factor.

+ Factor not considered in the candidate set of variables for the wrist model due to presence of missing data above the pre-determined cut-off of up to 30% data missing.

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Table 6: Validation of optimum SONAR and SONAR 12M models against primary fistula failure and assisted primary fistula failure at 6 months

	SONAR models	SONAR-12M models
Against primary fistula failure at 6 months		
PPV for optimum wrist model (95% CI)	31.8% (18.1 – 45.6)	72.7% (46.4 – 99.0)
NPV for optimum wrist model (95% CI)	94.7% (87.6 – 100.0)	91.3% (84.7 – 98.0)
PPV for optimum elbow model (95% CI)	22.2% (6.5 – 37.9)	57.1% (20.5 – 93.8)
NPV for optimum elbow model (95% CI)	87.5% (78.8 – 96.2)	88.2% (80.9 – 95.4)
Against assisted primary fistula failure at 6 months		
PPV for optimum wrist model (95% CI)	31.6% (16.8 – 46.4)	29.3% (15.3 – 43.2)
NPV for optimum wrist model (95% CI)	95.5% (89.3 – 100.0)	100.0% (100.0 – 100.0)
PPV for optimum elbow model (95% CI)	14.3% (1.3 – 27.3)	17.9% (3.7 – 32.0)
NPV for optimum elbow model (95% CI)	94.5% (88.5 – 100.0)	96.4% (91.4 – 100.0)

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Figure Legends

Figure 1 legend:

Representative fistula venous diameter **(a)** & **(b)** and fistula volume flow rate **(c)** & **(d)** for elbow (a & c) and wrist (b & d) according to maturation status at week 10. Box and whisker plot shows minimum value (after excluding outliers), 25th centile, median, 75th centile and maximum value (after excluding outliers) without imputation of primary outcome. Fistulas that failed before week 10 (thrombosis or abandonment after a failure) were excluded from the analysis.

Stacked 100% bar charts showing the proportion of **(e)** elbow and **(f)** wrist fistulas, with the following outcomes at each of weeks 2, 4, 6 and 10: died; withdrawn; abandoned; thrombosed; mature by ultrasound parameters (at that scan), not mature by ultrasound parameters (at that scan), unknown (did not attend scan or where missing data from the scan prevented determination of maturity). **(g)** & **(h)**: as for (e) and (f) but for all fistulas, presented as numbers and including arrows depicting status at next scan of those fistulas mature **(g)** or immature **(h)** at previous scan.

Figure 2 Legend:

Scatter plot of representative venous diameter by average volume flow at 2, 4 and 6 weeks (figures a, b, and c, respectively) with different symbols for matured/not matured fistulas at week 10 (as per primary outcome with no imputation).

Figure 3 Legend:

Standard ROC curves for the optimum models establised for predicting week 10 fistula non-maturation from week 4 ultrasound findings for **(a)** elbow, and **(b)** wrist fistulas, with 1-specificity (x-axis) plotted against sensitivity (y-axis), and each point on the graph generated by using a different threshold point. The optimal threshold point chosen in our study is shown in the plot (Youden index, symbol "Y"); the threshold value is the number on the far left to the "Y".

Figure 4: Summary of week 4 ultrasound modelling on identifying 10-week fistula status

Figure 5 Legend:

Kaplan Meier analysis of primary, assisted primary, and secondary patency rates to 12 months for **a)** elbow and **b)** wrist AVFs. Numbers in brackets represent 12 month (+ 95% confidence interval) patency rates.

Figure 6 Legend:

Standard ROC curve analysis for the optimum models established for predicting 6-month fistula non-patency from **a)** week 6 ultrasound findings for wrist and **b)** week 4 ultrasound findings for elbow fistula, with 1-specificity (x-axis) plotted against sensitivity (y-axis), and each point on the graph generated by using a different threshold point. The optimal threshold point chosen in our study is shown in the plot (Youden index, symbol "Y"); the threshold value is the number on the far left to the "Y".

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Appendices

Appendix 1: Sonar Trial Group

Anna Sidders, Cara Hudson, Claire Foley, Valerie Hopkins, Emma Laing, Chloe Fitzpatrick-Creamer, Helen Thomas, Alison Deary (NHS Blood and Transplant Clinical Trials Unit).

Gavin J Pettigrew, James Richards, Mohammed Hossain, Dominic Summers, Matthew Slater, Laura Scott, Regin Lagaac, Veena Surendrakumar, Tobi Ayorinde, Igor Chipurovski, Manikandan Kathirvel, Manoj Thialli, Subhankar Paul, Andrew Norton (Cambridge University Hospital).

Simon Knight, Klaus Bond, Elizabeth Hardy, Joanne Widdup, Rachael Potter, Elisabeth Pugh, Karen Parsons, Kathryn Lafferty, Madita Gavrila, Sheera Sutherland, Ria Rabara (Oxford University Hospitals NHS Foundation Trust).

Rajesh Sivaprakasam, Kate Crawford, Amy Bolsworth, Naavalah Ngwa-Ndifor, Laura Clementoni (Bart's Health NHS Trust).

Reza Motallebzadeh, Mohammad Ayaz Hossain, Matthew Bartlett, Rani Badhan, Fernando Yuenchang, Phil Gardiner, Natasha Irani (Royal Free London NHS Foundation Trust).

Zia Moinuddin, Helena Edlin, Anna Jerram, Jessica Lai, Joyce Banda, Janet Bendle (Manchester University NHS Foundation Trust).

Sam Turner, Maria Morgan, William Owen, Sue Dawson, Simon Daniel, Karen Allsop (North Bristol NHS Trust).

Andrew Tambyraja, Sarah-Jane Carmichael, Tom Eadie, Rona Lochiel, Midel Lena, Karen Gallagher (Royal Infirmary of Edinburgh, NHS Lothian).

Nicholas Barnett, Soundrie Padayachee, Philip Eldridge, May Rabuya, Naomi Hare (Guy's & St Thomas' NHS Foundation Trust).

Subash Somalanka, Jashree Patel, Abbas Ghazanfar, Judy van Selm, Caroline Bodneck, Martia Augustin, Kwame Ansu, Nalin Khosla, Kashif Burney, Karen Dear, Duminda Basnayake, Laijee Benny (Epsom and St Helier University Hospitals NHS Trust).

James Hunter, Carl Tiivas, Samantha Hyndman, Maria Truslove, Gail Evans, Kerry Read (University Hospital Coventry and Warwickshire NHS Trust).

Sam Dutta, Andrew Beech, Sarah Brand, Tara MacCormick-Swanson (Nottingham University Hospitals NHS Trust).

Sarah Lawman, Darren Cheal, Mel Smith, Kate Trivedi, Valentina Toska, Lorraine Shah-Goodwin (Brighton & Sussex University Hospitals NHS Trust).

Tracey Salter, Adnan Bajwa, John Kerr, Ana Fleet, Lianne Chapman, Sarah Gee, Thanuja Weerasinghe, Lisa Kavanagh, Louise Rowe-Leete (Frimley Health NHS Foundation Trust).

George Smith, Paris Cai, Judith Long, Tracey Rowe (Hull University Teaching Hospitals NHS Trust).

Mohammed Aslam, Jeremy Crane (Imperial College Healthcare NHS Trust).

Atul Bagul, Mary Quashie-Akponeware, Kate Waters, Alexandra Howson (University Hospitals of Leicester NHS Trust).

Neil Hoye, Alycon Walker (South Tees Hospitals NHS Foundation Trust)

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Appendix 2: Author Contributions

James Richards (Locum Consultant in NORS, HPB and Transplant Surgery) was involved in the conception and design of the study, patient recruitment and data acquisition, and drafting of the report.

Dominic Summers (Consultant Transplant and Vascular Access Surgeon) was involved in the conception and design of the study, data acquisition, and drafting of the report.

Anna Sidders (Trial Manager) was involved in the conception and design of the study and drafting of the report.

Elisa Allen (Trial Statistician) was involved in the conception and design of the study, analysis and interpretation of the data and drafting of the report.

Helen Thomas (Head of Clinical Trial Statistics) was involved in the conception and design of the study, analysis and interpretation of the data and drafting of the report.

Mohammed Ayaz Hossain (Consultant Transplant Surgeon) was involved in the conception and design of the study, data acquisition, and drafting of the report.

Subhankar Paul (Senior Clinical Fellow in Transplant Surgery and Organ Retrieval) was involved in the conception and design of the study, data acquisition, and drafting of the report.

Matthew Slater (Vascular Scientist) was involved in the conception and design of the study, ultrasound data acquisition and drafting of the report.

Matthew Bartlett (Vascular Scientist) was involved in the conception and design of the study, ultrasound data acquisition and drafting of the report.

Regin Lagaac (Renal and Vascular Access Nurse) was involved in the conception and design of the study, data acquisition, and drafting of the report.

Emma Laing (Clinical Operations Manager) was involved in the conception and design of the study and drafting of the report.

Valerie Hopkins (Clinical Trial Coordinator) was involved in the conception and design of the study and drafting of the report.

Chloe Fitzpatrick-Creamer (Clinical Trial Administrator) was involved in the conception and design of the study and drafting of the report.

Cara Hudson (Trial Statistician) was involved in the conception and design of the study, analysis and interpretation of the data and drafting of the report.

Joseph Parsons (Trial Statistician) performed statistical analysis and interpretation of the data and drafting of the report.

Sam Turner (Consultant Renal Transplant and Vascular Access Surgeon) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting the of report.

Andrew Tambyraja (Consultant Vascular Surgeon) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Subash Somalanka (Consultant Nephrologist) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

James Hunter (Consultant Renal Transplant and Vascular Access Surgeon) is a Grant Co-applicant and Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Sam Dutta (Consultant Transplant and General Surgeon) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

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Neil Hoye (Consultant Nephrologist) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Sarah Lawman (Consultant Nephrologist) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Tracey Salter (Consultant Nephrologist) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Mohammed Aslam (Clinical Vascular Scientist) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Atul Bagul (Consultant Transplant and Endocrine Surgeon) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Rajesh Sivaprakasam (Consultant Transplant Surgeon) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

George Smith (Honorary Consultant Vascular Surgeon) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Zia Moinuddin (Consultant Transplant Surgeon) is a Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Simon Knight (Honorary Consultant Transplant and Vascular Access Surgeon) is a Grant Co-applicant and Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Nicholas Barnett (Consultant Transplant and Vascular Access Surgeon) is a Grant Co-applicant and Principal Investigator involved in the conception and design of the study, data acquisition and drafting of the report.

Reza Motallebzadeh (Consultant Renal Transplant Surgeon) is a Grant Co-applicant and Principal Investigator involved in the conception and design of the study, data acquisition, and drafting of the report.

Gavin J Pettigrew (Professor of Clinical and Experimental Transplantation) is the Grant Lead Applicant and Chief Investigator responsible for the conception and design of the study, data acquisition, the analysis and interpretation of the data and writing the report.

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Figure 1: Ultrasound scan findings at 2, 4, 6 & 10 weeks following fistula creation.

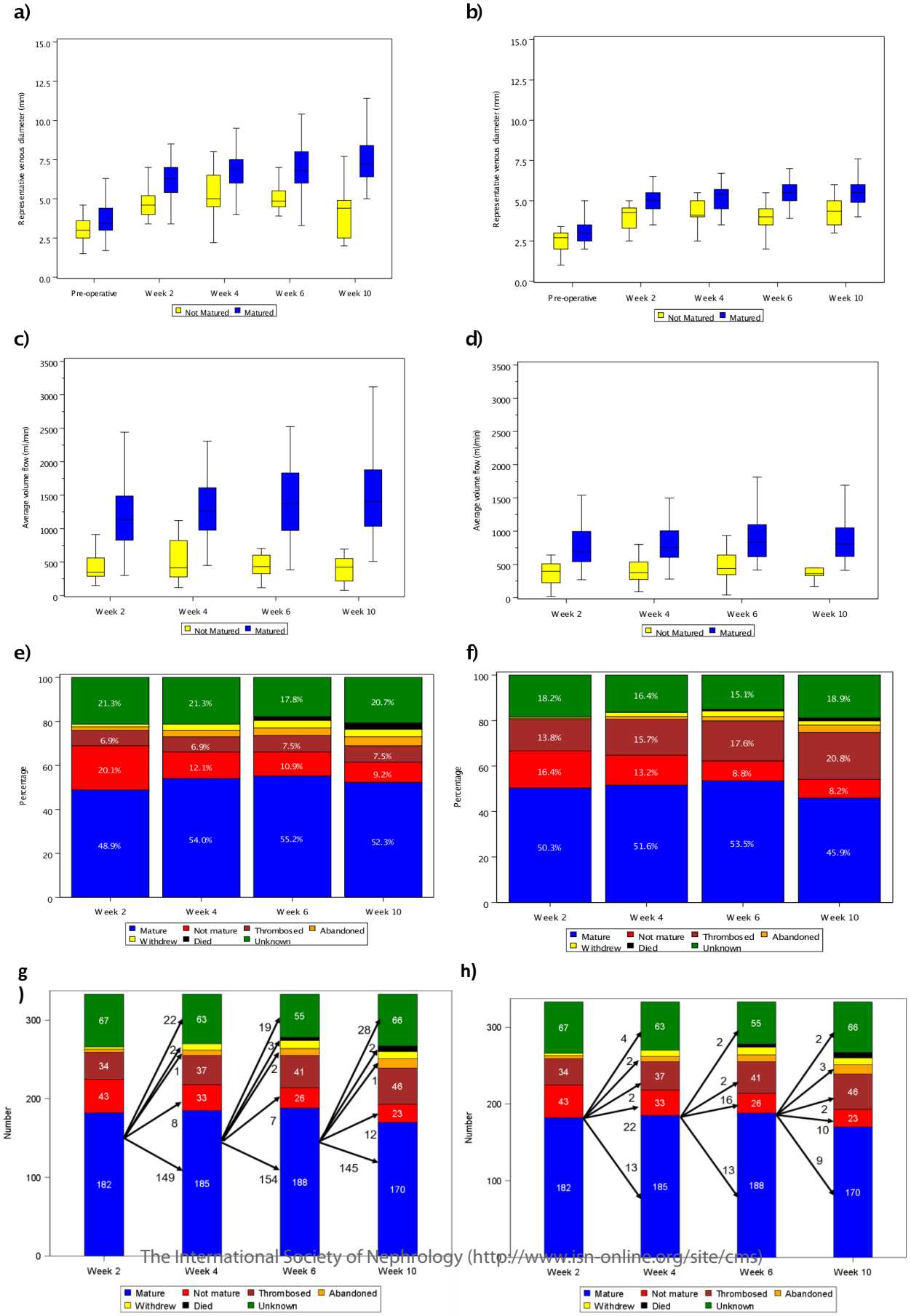

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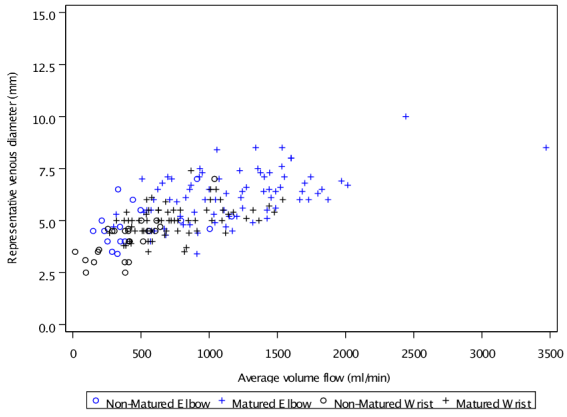
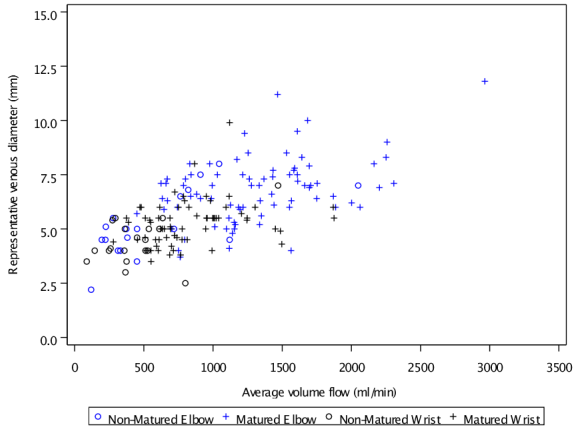
Figure 2: Scatter plot of representative venous diameter by average volume flow at each scan time-point, according to fistula site and maturation status at week 10.

a)



b)



c)

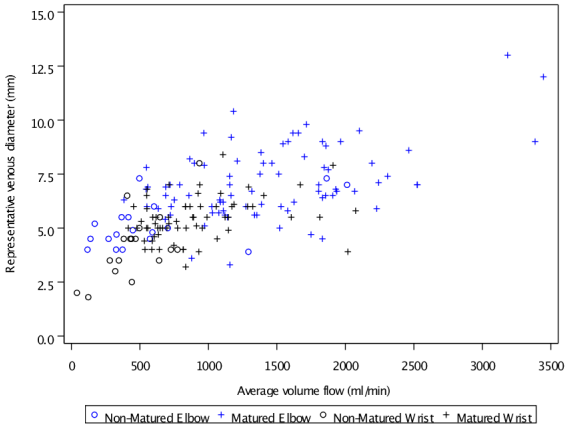
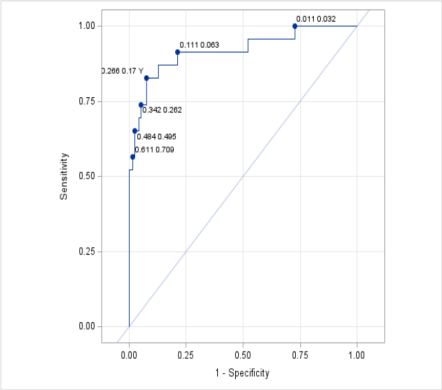


Figure 3: Receiver Operating Characteristic (ROC) curve analysis of optimum models for predicting fistula non-maturation at week 10.

a)



b)

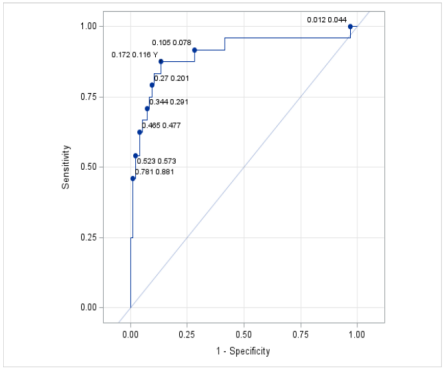
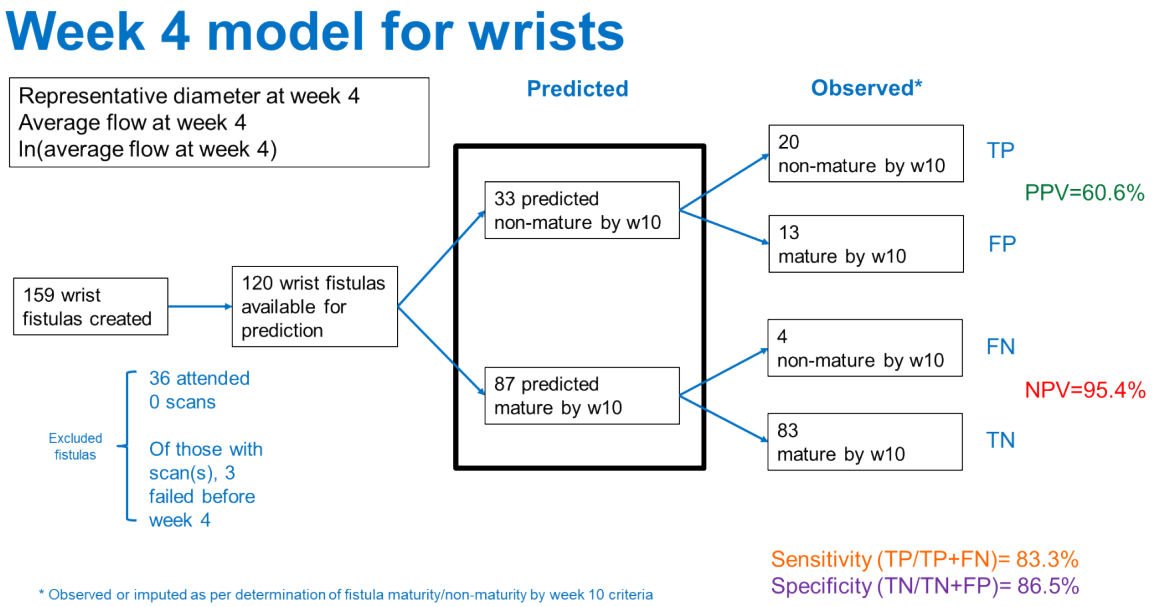


Figure 4: Summary of week 4 ultrasound modelling on identifying 10 week fistula status



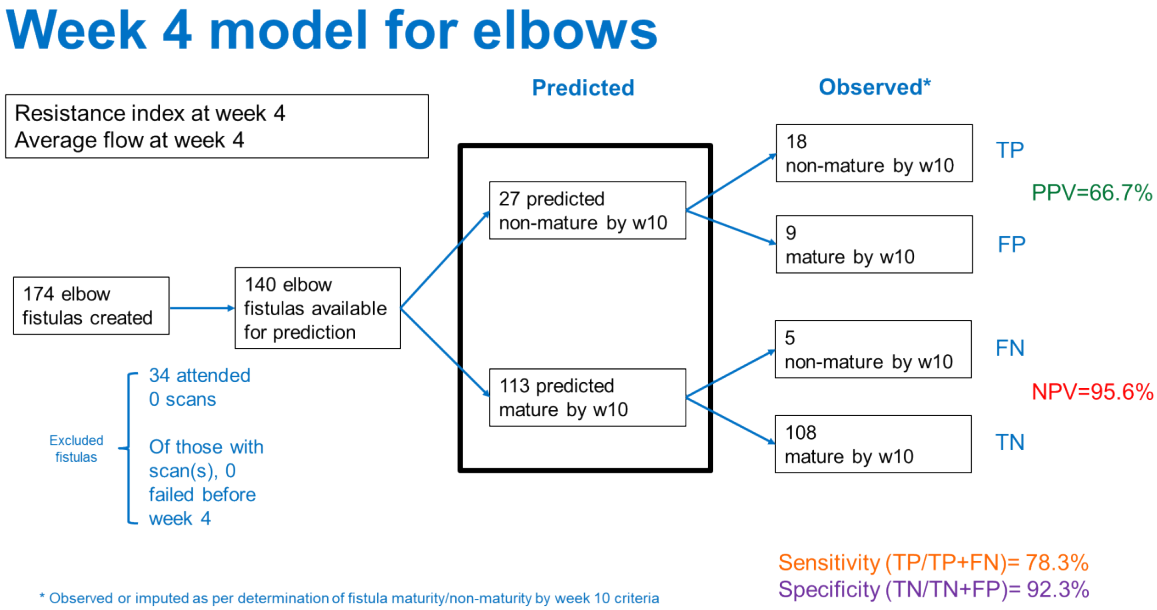
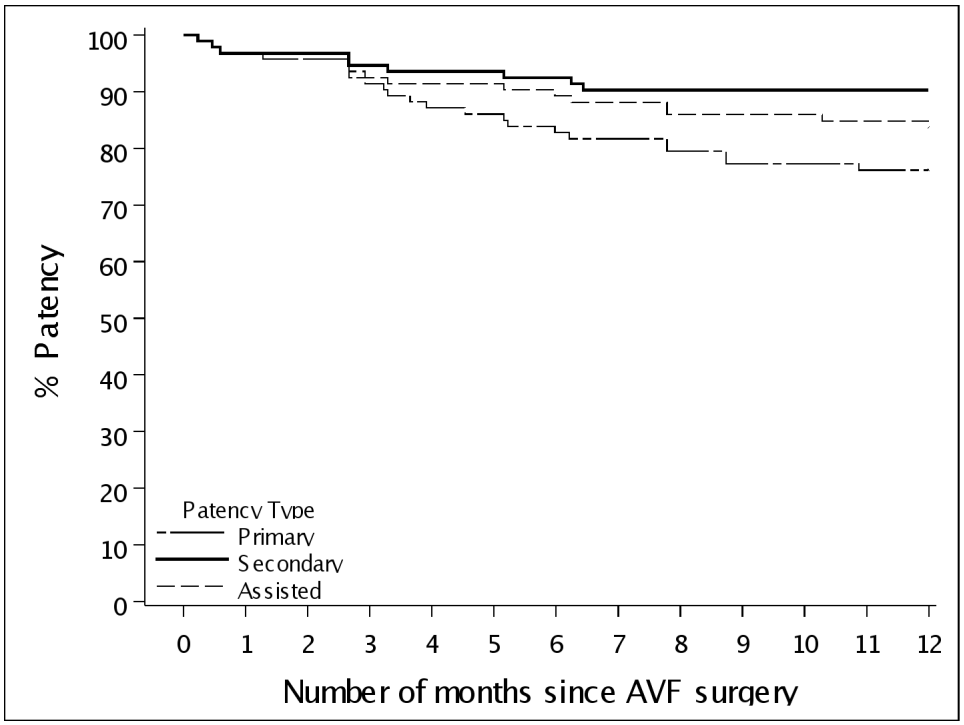
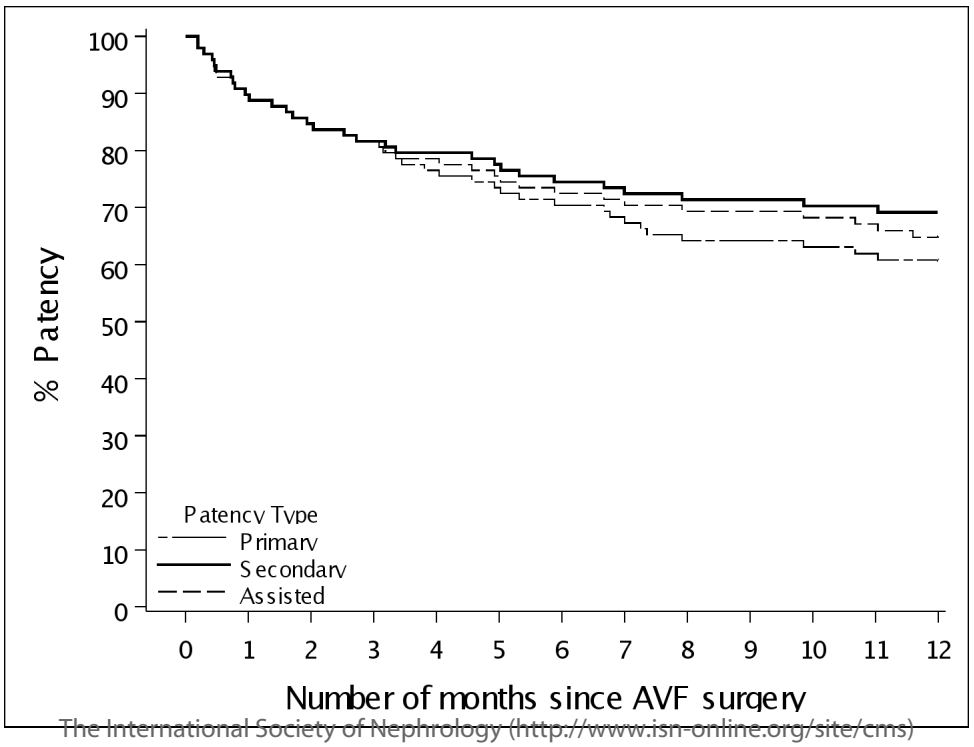


Figure 5: Kaplan Meier analysis for 12 month AVF patency

a)



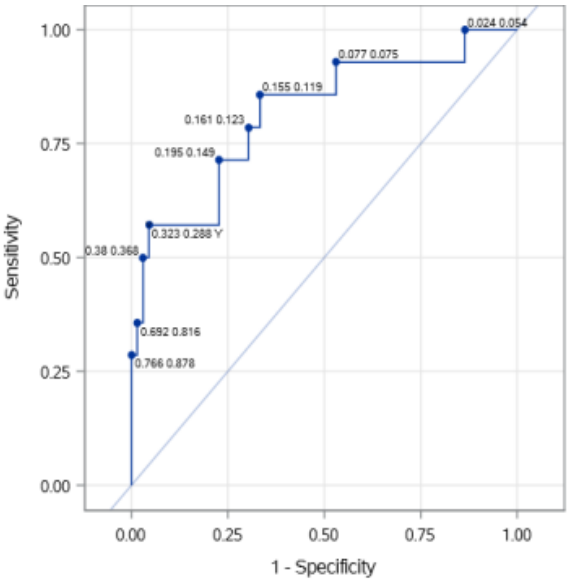
b)



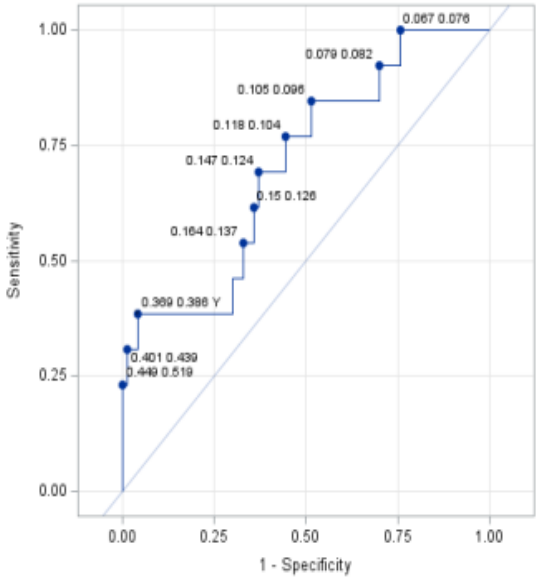
The International Society of Nephrology (http://www.isn-online.org/site/cms)

Figure 6: Receiver Operating Characteristic (ROC) curve analysis of optimum models for predicting a) wrist and b) elbow fistula non-patency at 6 months.

a)



b)



Supplemental Material

Supplementary Methods

Missing Data

In anticipation that some participants would be unable to attend all scans and that some scan data would therefore be missing, the following assumptions were adopted:

If the primary outcome data was missing (i.e. the fistula volume flow and / or representative venous diameter on the week 10 scan was unavailable) then:

1. If at least one scan had occurred at weeks 2, 4 or 6 and fistula maturity was achieved by ultrasound criteria at the latest available time-point, it was assumed that the fistula was *mature* at week 10.
2. If fistula non-maturity was consistently reported at weeks 2, 4 and/or 6, or at least one scan at weeks 2 or 4 confirmed fistula maturation, but a later scan reported non-maturation then fistula *non-maturation* was imputed at week 10, ***unless*****,** for dialysis patients, the fistula has been used successfully at least once or, for pre-dialysis patients, was deemed suitable for dialysis cannulation on clinical examination; in these instances fistula *maturity* at week 10 was imputed.
3. If the fistula was abandoned because of development of steal syndrome or pseudoaneurysm within the study period (reported in the end of study form) and with at least one scan form available, then 10-week fistula status was imputed as per (1) or (2).
4. If the participant died within the study period (reported in the end of study form) and with at least one scan form available, then 10-week fistula status was imputed as per (1) or (2).

For fistula flow and venous diameter at the 2-, 4- and 6-week scans, as well as for other factors considered in modelling of primary fistula maturity, missing data was imputed using multiple imputation techniques if the level of missing data was greater than 10% but less than 30%. Any factors with greater than 30% missing data were excluded from the analysis. Any data for factors with less than 10% missing data were not imputed and used directly in the analysis. In general, attendance for the ultrasound scans was good; 126 (37.8% of those with an AVF created) participants missed an expected scan, but at any particular time point approximately three-quarters of participants attended for the scheduled scan resulting in acceptable data completeness. For the optimum models selected for primary fistula maturation, a sensitivity analysis was additionally performed, excluding any imputed outcome. Outcomes (fistula maturation at 10 week) were imputed on 16.8% (56 patients).

If primary fistula patency at 6 months could not be determined from reported data, it was imputed as follows:

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1. If there was evidence in the data that the fistula had been used for haemodialysis at 6 months after fistula creation, without interventions, then the fistula status was imputed as patent at 6 months.
2. In other cases, primary fistula patency was imputed by clinical review, including for those participants who underwent a transplant. For instance, if the last known follow up of the fistula was at 3 months post creation and a patent status was reported (e.g. through use of the fistula for haemodialysis or palpable thrill in comment boxes), then the fistula status was imputed as patent at 6 months, subject to detailed clinical scrutiny of the case.

For fistula flow and venous diameter at the 2-, 4- and 6-week scans, as well as for other factors considered in modelling of primary fistula patency, missing data was imputed using multiple imputation techniques as before.

Missing secondary outcome data was not imputed.

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Doppler ultrasound protocol

Surveillance Of arterioveNous fistulAe using ultRasound

SONAR STUDY - Arterio-venous Fistula (AVF) Duplex Examination Brief Protocol

Each patient will be given a trial number and this will enable images to be anonymised.
Within the Patient ID field and surname field please type SONAR followed by the trial number.

- Scan from the proximal artery up to and including the outflow deep vein.
- Within the Brachial artery measure volume flow (over 3 cardiac cycles) in roughly the same place three times and record.
- Within the Brachial artery measure the Resistance index (over 1 cardiac cycle) three times and record.
- Measure the outflow AVF at its smallest point, largest point and give a representative size of the majority of the AVF.
- Measure the depth of the outflow AVF (within the area that would be used for dialysis) at its shallowest point, deepest point and give a representative depth of the majority of the outflow vein.
- Measure the diameter and the PSV at the anastomosis.
- Assess for stenosis or any other pathology.
- Grade type of stenosis in the outflow vein using the criteria below;

Type 1 – Vessel diameter

Type 2 – Vessel diameter and intimal hyperplasia

Type 3 – Intimal hyperplasia

Type 4 – Thrombus

Type 5 – Valve

Type 6 – Other or not able to identify

Ignore any branches/Perforators unless in the opinion of the Sonographer they are draining substantial flow away from the main outflow vein. If there is a substantial branch note this in the written report and detail on the diagram.

The following images should be recorded as a minimum:

- **Volume flow x3** within the brachial artery
- **Resistance index x 3** within the brachial artery
- **Outflow vein diameters** (maximum, minimum and representative)
- **AVF depth** (shallowest, deepest and representative)
- **PSV and diameter at the anastomosis**
- **PSV at any stenosis**, and prior to stenosis
- **Any other pathology**

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The minimum number of images for each scan will depend on whether the machine will allow volume flow and RI to be calculated on the same image.

If the machine allows RI and Volume flow on the same image the minimum images will be 11.
If the machine does not allow RI and Volume flow on the same image the minimum images will be 14.

Image Labelling

Acceptable abbreviations are in brackets.

Axillary artery (AX A, Axillary A) – Only if needed in the event of a very high Brachial Bifurcation
Brachial artery (BA, Brachial A)
Radial artery (RA, Radial A)

Proximal (Prox, P)
Distal (Dist, D)

It is acceptable to use proximal and distal within the context of arteries as normal (e.g BA prox) but please do not use these in the context of the AVF.

Anastomosis (Anas)
Cephalic vein lower arm (CV LA)
Cephalic vein upper arm (CV UA)
Basilic Vein UA (BV UA)

If the name of the vein is unknown then it is acceptable to use the label AVF. Any branches may be labelled AVF Branch or Cephalic vein branch etc.

Any other pathology can be named by its description e.g. Pseudoaneurysm, Seroma etc. and its location e.g. Anterior to Radial artery.

After the Scan

Complete a blank SONAR AVF ultrasound proforma.

Log in to the electronic Case Report Form (MACRO) and enter the data. Keep completed proforma in the SONAR Ultrasound file provided by the study team.

Ensure images are stored in case of audit, but ensure this is offline and that the clinical team do not have access to the images to ensure they remain blinded.

DO NOT inform the patients of the results (to ensure they do not bias clinicians by passing on the findings).

However, if the AVF is occluded please inform the clinical team at your centre ASAP.

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Supplementary Tables

Table s1: Primary outcome following AVF creation, considered at each scan time-point.

	All fistulas		Elbows		Wrists	
	n/N	%	n/N	%	n/N	%
Fistulas with primary outcome data reported	249/333	74.8%	125/174	71.8%	124/159	78.0%
Fistulas with primary outcome data imputed	56/333	16.8%	29/174	16.7%	27/159	17.0%
Primary fistula maturity by week 10 (95% CI)	**219/333**	**65.8% (60.4-70.9)**	**117/174**	**67.2% (59.7-74.2)**	**96/159**	**60.4% (52.3-68.0)**
Fistulas with a failure event before, or at, 2 weeks after AVF creation ('early failures')	37/333	11.1%	13/174	7.5%	24/159	15.1%
Fistulas patent after 2 weeks[1]	296/333	88.9%	161/174	92.5%	135/159	84.9%
Primary fistula maturity by week 10 for patent fistulas after 2 weeks (95% CI)	219/296	74.0% (68.6-78.9)	117/161	72.7% (65.1-79.4)	96/135	71.1% (62.7-78.6)
Fistulas with a failure event before, or at, 4 weeks after AVF creation	40/333	12.0%	13/174	7.5%	27/159	17.0%
Fistulas patent after 4 weeks[1]	293/333	88.0%	161/174	92.5%	132/159	83.0%
Primary fistula maturity by week 10 for patent fistulas after 4 weeks (95% CI)	219/293	74.7% (69.4-79.6)	117/161	72.7% (65.1-79.4)	96/132	72.7% (64.3-80.1)
Fistulas with a failure event before, or at, 6 weeks after AVF creation	46/333	13.8%	15/174	8.6%	31/159	19.5%
Fistulas patent after 6 weeks[2]	287/333	86.2%	159/174	91.4%	128/159	80.5%
Primary fistula maturity by week 10 for patent fistulas after 6 weeks (95% CI)	219/287	76.3% (71.0-81.1)	117/159	73.6% (66.0-80.3)	96/128	75.0% (66.6-82.2)

Note that 6 elbow fistulas met the 'all fistula' criteria for maturity (representative venous diameter ≥4mm and average volume flow >400 mls/min), but did not meet the 'elbow' criteria for maturity (representative venous diameter ≥5mm and average volume flow >500 mls/min).

[1] fistulas that are patent at the reported time-point but that did not reach maturity by week 10 include those that: will fail between the reported time-point and week 10; remain patent but do not reach maturity by week 10; whose 10 week outcome is unknown.

[2] There are 68 (=287-219) fistulas, under the 'all fistula' criteria, that were patent after 6 weeks but did not achieve maturity by week 10: 11 failed subsequent to the week 6 scan; 29 remained patent but 'non-mature'; and 28 whose week 10 outcomes are unknown (**Table 3**).
For the 42 elbow fistulas that were patent after 6 weeks but did not achieve maturity by week 10:
3 failed after week 6; 19 remained patent but 'non-mature'; and 20 have an unknown outcome (**Table 3**).
For 32 wrist fistulas that were patent after 6 weeks but did not achieve maturity by week 10:
8 failed after weeks 6; 16 remained patent but 'non-mature' and have an unknown outcome (**Table 3**).

Table s2 Ultrasound scan data

Elbows	N	Median	Interquartile range	Range
Representative venous diameter (mm)				
Pre-operative	144	3.4	2.9 - 4.45	0.4 - 11
At day 14	119	6	5 - 7	0.6 - 10
At day 28	115	6.5	5.6 - 7.5	0.6 - 11.8
At day 42	115	6.7	5.7 - 8	3.3 - 13
At day 70	106	7	6 - 8	2 - 12
Average volume flow (ml/min)				
At day 14	120	1012	664 - 1432.5	37 - 3471
At day 28	115	1173	821 - 1610	119 - 2965
At day 42	115	1211	751 - 1832	117 - 3446
At day 70	107	1333	832 - 1811	78 – 3267
Average resistance index				
At day 14	119	0.48	0.4 - 0.54	0.17 - 0.92
At day 28	115	0.47	0.4 - 0.53	0.29 - 0.87
At day 42	115	0.47	0.4 - 0.53	0.24 - 0.82
At day 70	106	0.46	0.4 - 0.52	0.28 - 6.1
Wrists	N	Median	Interquartile range	Range
Representative venous diameter (mm)				
Pre-operative	90	3	2.2 - 3.2	1 - 5
At day 14	107	5	4 - 5.4	2.5 - 7.4
At day 28	104	5	4.35 - 5.5	2.5 - 9.9
At day 42	99	5.1	4.4 - 6	1.8 - 8.4
At day 70	86	5.5	4.5 - 6	3 - 8.8
Average volume flow (ml/min)				
At day 14	106	609.5	417 - 867	17 - 1710
At day 28	104	707	511.5 - 995	87 - 1875
At day 42	99	748	549 - 990	40 - 2075
At day 70	87	775	514 - 999	166 - 1934
Average resistance index				
At day 14	107	0.52	0.44 - 0.62	0.2 - 1
At day 28	105	0.53	0.45 - 0.6	0.28 - 0.84
At day 42	99	0.53	0.44 - 0.61	0.22 - 17.69
At day 70	87	0.52	0.43 - 0.6	0.21 - 0.81

Table s2 presents descriptive statistics for representative venous diameter, average volume and average resistance index at the different scan time points.

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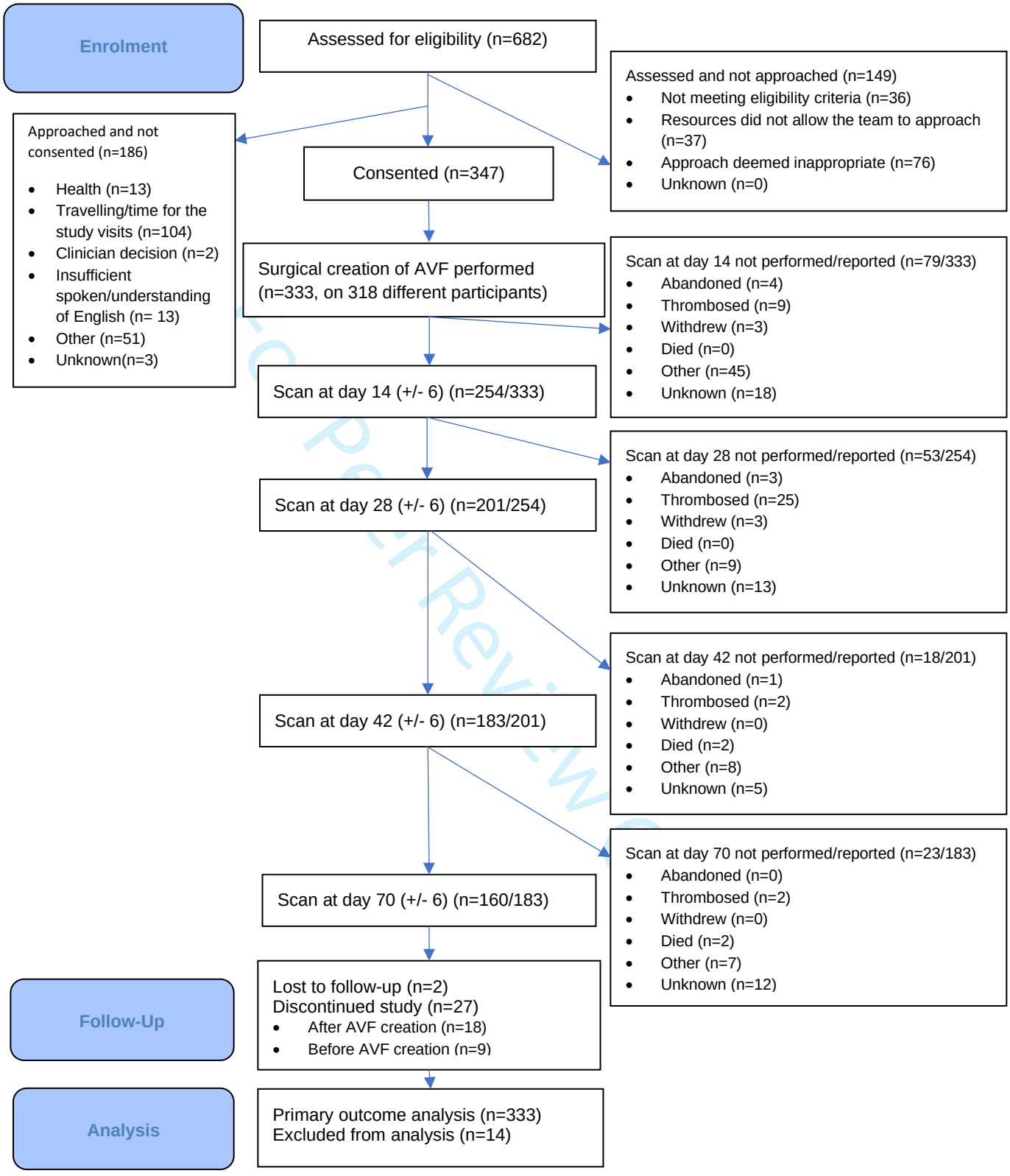
Supplementary Figures

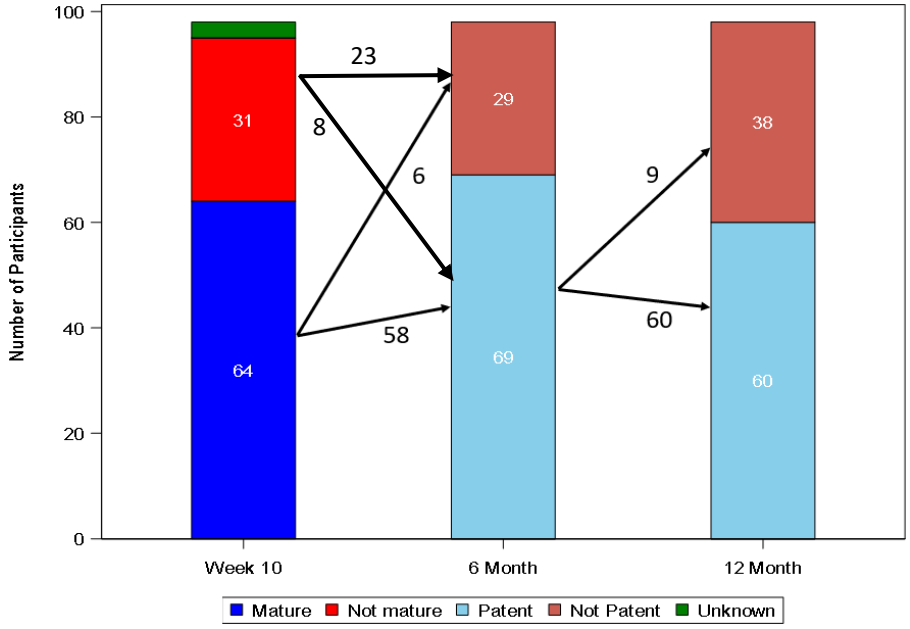
Figure s1 Study CONSORT diagram



Note that once a patient misses a scan, they do not proceed through the diagram, even though some of these patients did return for later scans. For example, the total number of expected day 70 scans reported was 201, but only 160 of these had attended all previous scans.

Figure s2: Fistula status at key study time-points

a) Wrists



b) Elbows

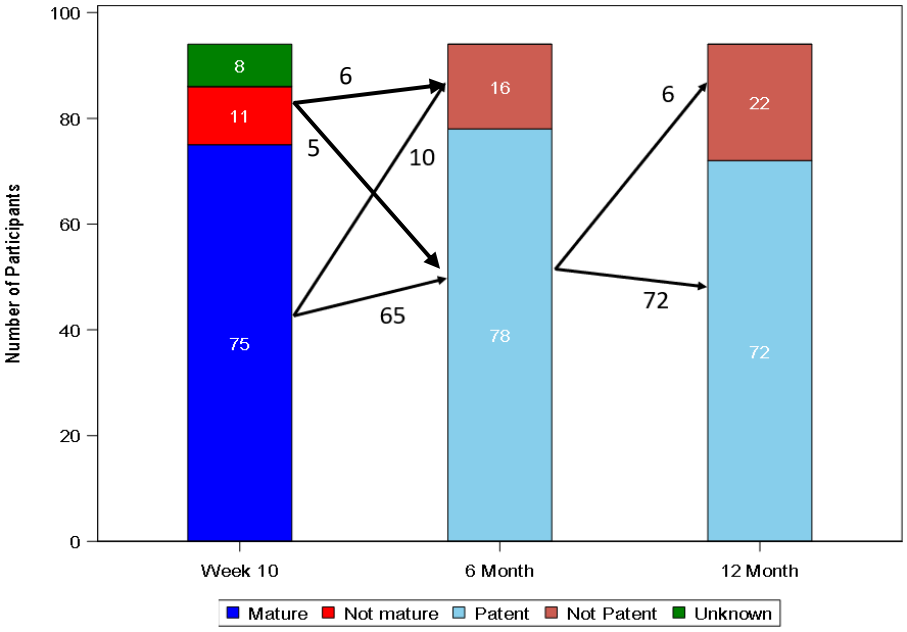


Figure s2 Legend

Fistula status at 10 weeks, and 6 and 12 months for **a)** wrist and **b)** elbow AVFs, with arrows depicting the transition of AVFs to the different categories at next study time-point. Fistula status depicted according to *imputed* data (see supplementary methods) with AVFs at 10 weeks being classed as mature or not mature (patent and not reached maturity or thrombosed / failed) and at 6 and 12 months as either patent or not patent.

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STROBE statement

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies*** 4
Early ultrasound surveillance of newly-created haemodialysis arteriovenous fistula:

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7 &. suppl
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	Suppl
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9

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		(c) Consider use of a flow diagram	x
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 3 Figure 6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Standard in results
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	supp
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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