

# Doppler ultrasound surveillance of recently formed haemodialysis arteriovenous fistula: the SONAR observational cohort study

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Published May 2024  
DOI: 10.3310/YTBT4172

## Scientific summary

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Health Technology Assessment 2024; Vol. 28: No. 24  
DOI: 10.3310/YTBT4172

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# Scientific summary

## Background

Because of their favourable durability and low infection rates, arteriovenous fistulas (AVFs) are considered the best option for provision of haemodialysis, and they offer survival advantages compared to dialysis through a central venous catheter (CVC). Upon surgical creation, AVFs undergo a period of 'maturation', wherein the transit of high-pressure arterial flow through the anastomosis triggers compensatory dilatation and thickening of the draining fistula vein, with marked increases in blood flow through the AVF. This maturation, which generally takes about 2 months, is required to achieve functionality and enables the AVF to be used for dialysis. The main drawback with AVFs is that a large proportion (in excess of 30% in some series) do not develop fully, and either thrombose or remain patent in an immature state. This necessitates further surgical or radiological interventions to aid maturation, or formation of an entirely new fistula, thus potentially prolonging the requirement for dialysis through a CVC. Strategies to increase maturation rates and early patency of AVFs may therefore make a substantial difference to patient outcomes. In this respect, widespread patient and clinician consultation, supported by the James Lind Alliance, has identified the question, 'What can be done to make fistulas or grafts last as long as possible?' as one of the top 10 research priorities in vascular access provision.

One possible approach to counter early fistula loss from non-maturation/thrombosis is to use Doppler ultrasound (US) surveillance in the first few weeks after creation to identify at-risk fistulas and to inform early radiological or surgical intervention, in anticipation that this improves longer-term fistula patency. This has, however, not yet been tested. The SONAR consortium, representing 17 UK centres that provide vascular access surgery, was established to test the hypothesis:

*Doppler US surveillance of AVFs immediately after creation improves longer-term AVF patency, by directing early and effective surgical or radiological salvage of those AVFs at risk of failing or not maturing.*

## Objectives

In considering the above hypothesis, several conditions must be met if US-guided early salvage intervention is to improve outcomes following AVF creation:

1. that US can effectively distinguish those newly formed fistulas that are unlikely to mature
2. that maturity failure occurs commonly enough that clinically meaningful improvements in fistula outcomes by early identification of at-risk fistulas are plausible
3. that salvage interventions performed on those 'at-risk' fistulas are effective and improve fistula patency.

The SONAR study thus aimed to address the following objectives sequentially, over a 5-year window:

1. Run an observational cohort study in which consenting participants undergo serial US assessment of their AVF in the first 3 months after its formation (phase 1).
2. Model whether features on early US can reliably identify those fistulas that will not mature or will fail early.
3. Assess from the observational cohort study whether a randomised controlled trial (RCT) evaluating early US-guided salvage intervention is feasible.
4. Run a multicentre RCT in which 1-year fistula patency in a treatment group receiving early US surveillance of their developing fistula is compared against standard care: monitoring of fistula maturation by clinical assessment only (phase 2).

Progression to the phase 2 study depended upon accomplishing the first three objectives and, in particular, demonstrating that US surveillance could accurately predict fistula non-maturation. This manuscript will thus focus on the phase 1 study set-up and outcomes.

## Methods

A prospective multicentre observational cohort study of adult patients undergoing formation of AVF for haemodialysis was performed to test the hypothesis:

*Doppler US surveillance early after AVF creation can reliably identify those AVFs that will not mature or will fail early.*

Criteria for participation were as follows:

1. Adult, aged 16 years or older.
2. The participant had end-stage renal disease and was either already established on haemodialysis or likely to start imminently.
3. The participant was due creation of an arm AVF (either wrist or elbow) including the following types of fistula: radiocephalic, ulnobasilic, brachiocephalic and brachiobasilic (one- or two-stage) fistula, with a minimal acceptable threshold of 2 mm venous diameter at whatever site was chosen.
4. Full informed consent to participate was provided.

Consenting participants underwent serial US scanning at weeks 2, 4, 6 and 10 after fistula formation in addition to standard care (such as regular clinical assessment) as per local centre policy. Fistula flow rates, fistula venous diameter and resistance index were recorded, according to a standard study protocol, with clinical teams blinded to the US findings, unless a scan was simultaneously requested on clinical grounds or the scan confirmed thrombosis of the fistula.

The primary outcome measure was fistula maturation at 10 weeks. To encompass participants who remained pre-dialysis, along with clinical examination, maturation was assessed at 10 weeks according to accepted surrogate US parameters:

- wrist fistula: representative venous diameter  $\geq$  4 mm, with flow  $>$  400 ml/minute
- elbow fistula: representative venous fistula diameter  $\geq$  5 mm, with flow  $>$  500 ml/minute.

Three distinct outcomes defined fistula non-maturation:

1. a fistula occlusion/thrombosis within the study period (76 days post AVF creation)
2. fistula abandonment within the study period due to failure to mature or due to thrombosis/occlusion
3. failure to achieve (either reported at the week 10 scan or imputed) maturation, according to the preset US parameters.

The following secondary outcome measures were also recorded:

1. for those patients established on dialysis, successful use of the fistula for dialysis on three successive occasions
2. clinical suitability for dialysis 10 weeks after fistula creation based on examination alone according to local practice
3. formation of a new fistula (including fashioning of proximal neoanastomosis) or radiological salvage procedure
4. fistula thrombosis

5. secondary fistula patency
6. patient acceptability, based on the proportion of patients that complete their scans.

Assuming that early US surveillance predicts fistula non-maturation/failure in 25% of AVFs, a total of 347 fistulas were required to achieve precision of  $\pm 10\%$  for an estimated 72% positive predictive value (PPV) for detecting non-maturation/failure. The total sample size allows for 10% dropout.

Mixed multivariable logistic regression (binary-data population-average model with exchangeable correlation structure) of the early US scan data was then used to build separate models for wrist and elbow AVF that contained the minimum number of measurements required to predict AVF non-maturation by 10 weeks. Receiver operating characteristic curves of the developed risk scores were analysed 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.

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 US 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 time 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 (at either week 4 or week 6) to effectively predict primary fistula non-patency at 6 months.

## Results

Of 347 consents to participation (median age 65 years; interquartile range 52–74 years; 64.8% male; 43.2% diabetic; 55.0% pre-dialysis), 333 underwent AVF creation during the study window (47.7% wrist, 52.3% elbow fistula). Early failure before the first US scan occurred in 37 (11.1%) AVFs, but by 10 weeks, 219 of 333 (65.8%) created AVFs had reached maturity (67.2% elbow, 60.4% wrist). Of the remainder, by week 10 a further 20 had failed (57 failures in total; 17.1%), 29 (8.7%) remained patent but not mature and the status of 28 (8.4%) was unknown. Excluding those failures occurring within the first 2 weeks (because it would be impractical to organise salvage so quickly) results in a fistula maturation rate of 74.0% at 10 weeks.

Serial US scanning revealed that maturation occurred rapidly (the vast majority of AVFs that were mature by 10 weeks had reached maturation by 2 weeks). Comparison of the early scan data in those AVFs that had matured by week 10 against those AVFs that remained immature (see [Figure 4](#)) revealed consistently lower fistula flow rates and fistula vein diameter in the latter. For example, the median blood flow at 2 weeks was 1135.5 and 691.0 ml/minute in those elbow and wrist fistulas, respectively, that reached maturation by week 10, whereas week 2 flows of 349.0 and 395.5 ml/minute were recorded in those elbow and wrist fistulas that did not reach maturation at week 10.

Modelling to predict AVF non-maturation at week 10 was optimally built on the week 4 scan data but required separate algorithms for wrist and elbow fistulas, with fistula venous diameter and flow rate at week 4 identified as the most significant variables in explaining wrist fistula maturity failure (PPV 60.6%,

95% CI 43.9% to 77.3%), whereas resistance index and flow rate were most significant for elbow fistula maturity failure (PPV 66.7%, 95% CI 48.9% to 84.4%). Diagnostic tests for model fit and influential observations were run on the optimum models for wrist and elbow AVFs, with both performing well, with area under the curve values of at least 0.90. Conversely, both models could predict fistula maturation much more reliably [NPVs of 95.4% (91.0–99.8) and 95.6% (91.8–99.4) for wrist and elbow, respectively].

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 US characteristics. Primary, assisted primary and secondary patency AVF rates at 6 months were 76.5%, 80.7% and 83.3%, respectively, and at 12 months were 68.3%, 74.1% and 79.5%, respectively. Broadly similar US characteristics (fistula vein size, flow rate and resistance index) were identified as the most significant variables predicting primary patency failure at 6 months, with similar predictive power as for 10-week AVF maturity failure, but with wide CIs (wrist AVF: PPV 72.7%, 95% CI 46.4% to 99.0%; elbow AVF: 57.1%, 95% CI 20.5% to 93.8%). Moreover, the models performed very poorly at identifying assisted primary and secondary patency failure, likely because a subset of those identified as liable to fail were instead successfully salvaged by radiological or surgical intervention.

## Conclusions

Although early US can predict fistula maturation and longer-term patency very effectively, it was only moderately good at identifying those unlikely to mature or to fail within 6 months. Allied to the better than expected fistula patency rate achieved by the SONAR consortium (that is further improved by successful radiological or survival salvage without recourse to the early US data), we estimate that a prospective randomised trial comparing early US-guided intervention against standard care (observation only) would require at least 1300 fistulas and would only achieve a minimally clinically important difference in the intervention arm if virtually every intervention were successful in maintaining/restoring fistula patency.

## Limitations

The US scan findings were generally not made available to the clinical teams, so as to avoid their influencing participant management. However, scan results were revealed to the responsible clinical team on 98 occasions (10.7% of all scans), either because an early US scan was standard care for that unit (76 occasions) or because unblinding was requested because of clinical concern relating to the fistula's maturation. It is therefore possible that in a small number of cases, the study US scans triggered salvage procedures that would not otherwise have been performed on clinical grounds alone. This is particularly problematic for the 12-month follow-up study, because the intervention would mark the end of primary patency – the primary outcome measure for the 6-month analysis – and it would therefore provide false support for the statistical modelling. However, in the majority of cases, unblinding did not prompt further intervention (simply instead confirming fistula maturation), and thus is unlikely to have compromised the statistical modelling.

Similarly, to include pre-dialysis patients in the study, it was necessary to adopt surrogate US markers to define fistula maturation, and it is perhaps not ideal to be using the same modality to delineate the maturation process as one uses to define maturation, particularly because fistula maturation is principally a functional concern relating to whether the fistula can be used to provide adequate dialysis. Repeat US was not performed at 6 months for the follow-up study, and the analysis of fistula patency, rather than maturation status, provides a better reflection of fistula functionality. This may partly explain the differences in the modelling findings between the 10-week and 6-month studies.

## Trial registration

The SONAR study was approved by the Cambridgeshire and Hertfordshire Research Ethics Committee and by the Health Research Authority (REC 18/EE/0234) and assigned ISRCTN36033877. The SONAR-12M study was approved by the West Midlands – Edgbaston Research Ethics Committee (REC 20/WM/0331) and assigned ISRCTN17399438.

## Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: NIHR135572) and is published in *full in Health Technology Assessment*; Vol. 28, No. 24. See the NIHR Funding and Awards website for further award information.





# Health Technology Assessment

ISSN 2046-4924 (Online)

Impact factor: 3.6

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## This article

The research reported in this issue of the journal was funded by the HTA programme as award number NIHR135572. The contractual start date was in May 2018. The draft manuscript began editorial review in November 2022 and was accepted for publication in June 2023. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

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