**Title (148 characters; 150 max)**

Graphical surveillance of kidney function data to reduce late presentation for kidney replacement therapy: a stepped wedge cluster randomised trial.

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**Running Title (30 characters; 35 max)**

Impact of eGFR graph reporting

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**Abstract (196 words)**

Late presentation for kidney replacement therapy (KRT) is an important cause of avoidable morbidity and mortality. We evaluated the effect of a complex intervention of graphical eGFR surveillance across 15% of the UK population on the rate of late presentation using data routinely collected by the UK Renal Registry.A stepped wedge cluster randomised trial was established across 19 sites. eGFR graphs were generated from all routine blood tests (community and hospital) across the population served by each site. Graphs were reviewed by trained laboratory or clinical staff and high risk graphs reported to family doctors. Due to delays outside the control of clinicians and researchers few laboratories activated the intervention in their randomly assigned time period, so the trial was converted to a quasi-experimental design.We studied 6100 end stage kidney disease (ESKD) events at 20 laboratories served by 17 main renal units. A total of 63,981 graphs were sent out. After adjustment for calendar time there was no significant reduction in the rate of presentation during the intervention period (0.90, 0.78-1.05, *P*=0.18). In conclusion, **i**mplementation of eGFR graph surveillance did not reduce the rate of late presentation for KRT after adjustment for secular trends.

**Key words (MeSH terms)**

Renal replacement therapy; chronic renal insufficiency; randomised controlled trial; quality improvement

**Lay Summary (214 words)**

“Late presentation” is when people with advanced chronic kidney disease are seen by specialist kidney services for the first time less than three months before they start dialysis or have a transplant. Late presentation leads to poorer outcomes for patients and higher healthcare costs.

We undertook a project aiming to reduce late presentation. We developed a computer programme which generated a graph of each patient’s kidney function over a period of time using the results of all their previous blood tests. Trained laboratory staff then reviewed the graphs. Where they saw a clear deterioration of kidney function over time the software sent a copy of the graph to the family doctor who had requested the latest blood test together with a prompt highlighting that further action, such as referral to kidney services, might be needed. We then tested whether our intervention was effective in a clinical trial across 15% of the UK population.

We found that highlighting patients with declining kidney function to family doctors using graphs did not significant reduce the late of late presentation when improvements over time across the whole country were taken into account.

In conclusion, graphical surveillance is an interesting and inexpensive intervention aimed at reducing late presentation, but more evidence is required before widespread adoption can be recommended.

**Introduction (297 words)**

Outcomes for patients with end-stage kidney disease (ESKD) are particularly poor in those who do not receive specialist care in time to prepare adequately for kidney replacement therapy (KRT), partly due to missed opportunities to create permanent vascular access, reduced access to home therapies and pre-emptive kidney transplantation,1,2 and increased costs of care.3 The 12-month mortality is 29% and 63% lower in patients presenting to kidney services more than 3 and 6 months respectively before the start of KRT.4

Although not all late presentation is avoidable, variation in its rate between countries and kidney centres suggests improvement is possible. In the Dialysis Outcomes and Practice Patterns Study between 2012-2014, the proportion of patients first seeing a nephrologist less than 4 months before starting hemodialysis varied from 13% in Sweden, 32% in the US, to 64% in China.5 In United Kingdom (UK) centres in 2013-2014, when this work was developed, the proportion first seen within 90 days of starting KRT varied from 5% to 34%.6

A modifiable risk factor for late presentation is delayed recognition of patients with progressive chronic kidney disease (CKD) in Primary Care.7 Implementation of community-wide reporting of graphical trends of estimated glomerular filtration rate (eGFR) to Primary Care by one kidney centre8 was followed by a decrease in the incident rate of KRT9 and the lowest percentage of patients presenting late in the UK.6 More robust evaluation was needed to determine whether this intervention was effective in other healthcare localities and contexts. We therefore implemented eGFR graph reporting across a population of 9.8 million people in England, Scotland, Northern Ireland and Wales to test whether a complex intervention built upon laboratory-based graphical surveillance of routine eGFR data reduces the rate of late presentation for KRT.

**Methods (1665 words)**

The ASSIST-CKD project (A programme to Spread eGFR graph Surveillance for the early identification, Support and Treatment of people with progressive CKD) was conceived and implemented as a stepped wedge cluster randomised trial (SWCRT) of an intervention during large-scale routine implementation.10 The design has been described in detail in a published protocol (International Standard Randomised Controlled Trials Number 13701669)11 and the findings are reported here in accordance with Consolidated Standards Of Reporting Trials guidance, and in particular the extensions covering the use of routinely collected data12 and SWCRT13 (see Supplementary Materials). The study was considered by the National Research Ethics Service (South East Coast-Surrey) and determined to be service evaluation, not requiring ethical review by an NHS Research Ethics Committee.11 A mixed methods evaluation was conducted; the qualitative findings have been reported separately.14

A process of targeted recruitment was initially followed based on data published by the UK Renal Registry (UKRR). Kidney centres with good completeness of late presentation data returns and a higher proportion of patients presenting late for KRT were approached, with preference given to those served by a single pathology laboratory. These criteria were subsequently relaxed, allowing recruitment at a regional level, e.g., all kidney centres in Wales and four out of five kidney centres in Northern Ireland. This approach offered efficiencies of scale and took advantage of a common laboratory IT infrastructure and shared priorities for improvement work.

The intervention was initially rolled-out sequentially with kidney centre clusters and their associated pathology laboratories receiving the intervention at staggered time points (“steps”). 19 sites were randomised to commence implementation at one of four six-monthly steps. In a SWCRT, crossover is unidirectional (from control to intervention) so all centres ultimately implement the intervention.

Financial support for participating sites covered the staffing costs of implementation for one year. It was expected that all on-costs from year two onwards would be met locally; support was offered by the project team to develop business cases for funding from local healthcare commissioners.

Randomisation was performed by the UKRR. Units of intervention (the laboratory) and outcome assessment (the kidney centre) were not always identical; UK kidney centres may provide services to more than one hospital laboratory, and a pathology laboratory may serve more than one kidney centre. Therefore, the unit of randomisation was defined as a system made up of a kidney centre together with the one or more laboratories that analysed blood tests for patients within that centre’s ESKD catchment population. Because renal units were served by multiple laboratories and laboratories crossed renal units, contamination within a renal unit was unlikely. Further details are provided in the Supplementary Materials.

There were delays in many cases due to local factors (for example availability of IT support and laboratory staff to review the graphs) before sites were able to confirm their interest in participating. As these factors were unrelated to the wider primary care/ nephrology services that influence most of the determinants of the primary outcome (and therefore are less important to balance through randomisation to minimise risk of bias) and also to minimise unacceptable delays to the timeline of the project for the funder, we took the pragmatic decision to perform randomisations at two time points. An initial randomisation was conducted when ten sites had confirmed. This randomisation, performed in June 2015 using random number generation (Statistical Analysis Systems, SAS), assigned four sites (from the ten) to the first step. The remaining six sites went to a second randomisation together with nine sites who confirmed their interest later. This randomisation, performed in October 2015 using the same methodology, assigned sites to one of the second, third and fourth steps. The research team and participating sites were not blinded to the results of the randomisations.

The intervention comprised three elements in addition to standard care: graphical presentation of patients’ eGFR results from routine blood tests; review of all graphs by trained laboratory or kidney staff; and reporting of selected graphs to Primary Care. The threshold for generating graphs was last eGFR <50 ml/min/1.73 m2 for patients aged 18-65 and<40 ml/min/1.73 m2 for patients aged >65 years.13 eGFR results from all settings, i.e., Primary Care/community and hospital, in the Laboratory Information Management System were imported into a structured query language (SQL) database and interrogated by a graphing software package (details in Supplementary Materials). Reports were intended to direct the attention of Primary Care Physicians (PCPs) to patients with progressive CKD. Criteria for progression were not fixed; instead, the training emphasised identifying individuals with a long-term trend towards ESKD within their lifespan. The report included a prompt to consider referral to nephrology but this was left to the PCP’s discretion. As this was a laboratory-based intervention the reporting staff were generally unaware whether the patient was already known to renal services. Staff had to pass a quality assurance test before reporting. The features of the intervention have been described in accordance with the Template for Intervention Description and Replication (TIDieR) checklist (see Supplementary Materials).

ASSIST-CKD was developed to provide evidence to support improvement in the care of patients with progressive kidney disease. The intervention was complex,15 targeting and attempting to change behaviour in multiple domains of the healthcare system, from PCPs and pathology laboratories through to specialist kidney services and commissioners of healthcare. Key process and outcome components were mapped against these elements in a Logic Diagram16 (**Figure 1**).

We recruited a diverse team of ten people to a dedicated patient project team. Members made key contributions to areas including: the development of a business case document and infographic for healthcare commissioners, which was led by our patient group; the presentation of powerful patient stories at our collaborative learning events; and the design of our qualitative evaluation.14

The primary outcome was late presentation for KRT, defined as less than 90 days between first nephrology clinic visit and first start of KRT (0 = early presentation; 1 = late presentation). Predefined secondary outcomes included: i) use of temporary vascular access at first start of KRT (0 = starting KRT with pre-emptive kidney transplant, peritoneal dialysis (PD) or hemodialysis (HD) via an arteriovenous fistula or graft; 1 = starting KRT on HD with a central venous catheter); ii) eGFR from two weeks preceding start of KRT (ml/min/1.73 m2); and iii) mortality at six months from first start of KRT (0 = alive at 6 months, 1 = died during 6 months after first start of KRT.

Outcome data were routinely collected by the UKRR. The UKRR directly collects, cleanses, analyses and reports data from all 61 adult and 12 paediatric kidney centres in England, Wales and Northern Ireland. It is assumed that all new ESKD events are captured by the UKRR. Further details are provided in the Supplementary Materials.

Box 1 summarises the study in Population Intervention Comparison Outcome (PICO) Format.

Statistical analyses were conducted at the UK Renal Registry using SAS version 9.4.

UKRR 2013 data from the first 12 centres estimated 46 patients per centre would commence KRT per year (range 20 - 88), with an average late presentation rate of 18% (range 9 - 35%); intra-cluster correlation (ICC) = 0.01 to 0.20. Four six-month control periods and six intervention periods of six months (one further control period, four intervention steps and one follow-up period), power 80%, alpha 0.05, and ICC 0.05, would detect a reduction in the average late presentation rate from 18% to 11%.17,18

The odds of late presentation were analysed at patient level using mixed-effects logistic regression, with kidney centre as a random effect (Model-1).19,20 This analysis was adjusted by time-period (step) (Model-2). Data were adjusted for patient demographics (age at start of KRT, gender, primary renal diagnosis, ethnicity and index of multiple deprivation quintile21) (Model-3). We also tested for interaction between time and treatment effect (Model-4). Model-2 was considered the primary result. Where necessary, sites were contacted to increase data completeness.

The following secondary outcomes were analysed: vascular access at the first start of KRT for any treatment modality and for hemodialysis using mixed-effects logistic regression; eGFR in the two weeks before first KRT using a mixed-effects linear regression model; and six-month mortality in new KRT patients in a mixed-effect logistic model. The same clustering approach was followed as that for the primary outcome.

It was anticipated that there would be a delay after implementation before an effect on late presentation would be seen. A lagged analysis was therefore performed whereby the first six months of the intervention period was treated as part of the control period. Additional analyses examined separately the first, second, and subsequent years of eGFR graph reporting.

Very few laboratories were able to activate the intervention in the period to which they were randomised, making the stepped wedge cluster randomised trial design11 no longer appropriate. As the delays in activating the intervention in laboratories were outside clinicians’ control (and therefore the timing of implementation of the intervention was unlikely be influenced by attitudes of the clinicians/clinical service, details in Supplementary Materials), the risk of bias was considered to be low and it was determined in September 2017 (ratified by the Evaluation Advisory Group on 11th June 2018) to convert to a quasi-experimental design. This required only one change to analysis plan - amending the time term in Models-2, 3 and 4 to adjust for calendar time only, rather than calendar and step time. The decision to convert to a quasi-experimental design also allowed the control cohort to be extended to include patients in non-participating kidney centres with data completeness for late presentation greater than 70% for each year of the study period of the incident cohort, and the addition of four intervention sites who were participating in a parallel project using the same intervention, outcomes measures, investigators and project management team funded by the East Midlands Strategic Clinical Network. The ASSIST-CKD ISRCTN record was updated to reflect these changes in May 2019 before any analysis had been conducted.

**Results (698 words)**

A total of 6100 new KRT events with referral data occurred between 1st January 2013 and 31st December 2019 from a final cohort including 20 laboratories serving 17 main kidney centres and covering a total population of 9.8 million people across the four Home Nations of the United Kingdom (14.6% of the mid-2020 UK population) (**Figure 2**). The level of data completeness was high: the Renal Registry receives data from all UK renal centres and individual patient postcode information (used to map patients to centres/laboratories) was available in over 99%.

The baseline characteristics of incident KRT cases are summarised in **Table 1**. The average rates of late presentation at ASSIST-CKD sites were 16.3% and 14.0% during control and intervention periods respectively, and 15.8% across the rest of the UK (**Table 2**). A total of 63981 graphs were sent out.

Considering the primary analysis, after adjustment for calendar time (Model-2, primary outcome) and for calendar time and patient demographics (Model-3) there was no statistically significant effect of the intervention on late presentation: Model-2 OR 0.90, 95% CI 0.78-1.05, *P* = 0.18; Model-3 OR 0.91, 95% CI 0.78-1.06, p=0.23 (**Table 2**). This was despite observing a reduction in the rate of late presentation during the intervention period in earlier unadjusted models (Model-1): odds ratio [OR] 0.85, 95% confidence intervals [CI] 0.74-0.98).

Similar results were obtained when treating the first six months after deployment as a control period and individually for the first, second, and third or more years of reporting (**Supplementary Table S1**).

The rates of late presentation between 2013 and 2019 for sites and the rest of the UK are presented in **Supplementary Table S2a**. The rate fell over time at ASSIST-CKD sites (OR 0.96 [yearly change], 95% CI 0.92-0.99) and across the rest of the UK (OR 0.98, 0.96-0.99) (**Supplementary Table S2b**). There was no interaction between change in late presentation rate over time and being an ASSIST-CKD site or rest of the UK site (data not shown).

The effect of the intervention varied across sites (**Table 3**). The percentage of patients presenting late was lower in the intervention than in the control period in 12/21 sites by -6.7 ± 1.3% (mean ± standard error [SE]) and higher in 9/21 sites by 4.4 ± 1.0% (mean ± SE). In the ten sites with the highest control rates, the rate was lower in eight, with a mean reduction across the ten of -5.4 ± 2.1% (mean ± SE).

The number of graphs reported to Primary Care each month per 10000 population ranged from 1.7 in Antrim to 16.7 in Truro (**Table 3**). For a typical list size of 2000 patients this equates to 0-4 graphs received by an individual GP per month. There was no relationship between reporting behaviour and change in late presentation rate.

There was no difference in the rates of permanent access in people receiving KRT or haemodialysis or in six-month mortality between the ASSIST-CKD sites (control and intervention periods) and the rest of the UK. The eGFR at KRT start was significantly higher during the intervention period but the magnitude of this effect was too small to be of clinical significance, and the data completeness for these data poor (45.8% for the ASSIST-CKD intervention period, 51.7% for the ASSIST-CKD control period, and 42.8% for the rest of the UK). The effect on these secondary outcomes did not change significantly with increased duration of graph reporting (**Table 4** and **Supplementary Table S3**).

The ASSIST-CKD project funded laboratories for one year but a majority of sites continued beyond this period. The intervention was deployed for a mean of 31 ± 3 (mean ± SEM) months (**Supplementary Table S4**). 13 of 20 sites were still live in March 2021; of these, two sites had been running for longer than five years, three further sites for longer than four years and three more for longer than three years. Reporting was embedded into routine practice and in yearly budgets in 12 sites. One site gained three years’ funding from their Primary Care Network. There was no increase in the number of referrals of new patients by Primary Care to five kidney centres with available data during the intervention period (data not shown).

**Discussion (1196 words)**

In this large multicentre trial including 6100 new ESKD events, the implementation of eGFR graph surveillance across 15% of the UK population did not reduce the rate of late presentation for kidney replacement therapy after adjustment for secular trends.

There is an important unmet need for targeted identification and early referral of the relatively small number of patients at high-risk of progressing to ESKD from the much larger number of people with kidney disease in Primary Care. This project tested a solution to this challenge that spans the boundary between research and quality improvement, blending digital healthcare with more traditional improvement methodology and using high quality routinely collected healthcare data to test the generalisability and transferability of an intervention previously only evaluated in a single centre.8,9

We have demonstrated that a complex intervention can be deployed at scale at the interface between Primary and Secondary Care. Successful deployment required significant barriers to be overcome, and most importantly the requirement for full buy-in from multiple stakeholders at the outset.14 In many sites there was a need for senior support to gain the local IT permissions to use third party software within the NHS environment; for sites in Wales and Northern Ireland, national-level support was required to achieve this. The intricacies of interfacing our software with different laboratory IT systems were often challenging, and in some cases required additional unfunded development work to be carried out by third parties. The availability of local staff (who were usually, although not exclusively, based in the laboratory) to review the graphs, was also a factor that delayed or prevented adoption at some sites.

The degree of complexity highlights the importance of local, regional and national contexts in determining its impact. The outcomes of this technological intervention were primarily determined by human behaviour: reporting behaviour, which was studied and varied substantially across sites; and the actions of the Primary Care Physicians and patients responding to the reports and the nephrologists managing newly referred patients, about which we know far less. It should therefore not be regarded as surprising that the impact of eGFR graph reporting varied across the intervention sites, with a suggestion that improvement in late presentation was greatest where it was most achievable and needed. Late presentation is a relatively blunt instrument to assess the impact of a system-wide intervention and other potential benefits, such as medication review, repeat testing, and patient education and shared decision making, have been described in a separate qualitative study of ASSIST.14 Questionnaires sent to family doctors at one site indicated that the eGFR graph reports were well-received, with practitioners often reviewing patients earlier than intended, checking local guidance and showing the graphs to their patients.22

The fact that the majority of sites continued to operate the reporting service after the program finished is evidence of its perceived value. From our previously published qualitative study of the ASSIST intervention at five sites, eGFR graph reporting did not seem to lead to an unacceptable increase in referrals to kidney centres14; a typical UK Primary Care Practice of 10000 patients received on average only two alerts per month. The costs of implementing eGFR graph reporting were modest: for a laboratory serving a population of 400000 with 60 new ESKD cases per year, the annual cost of approximately £10000 is much less than the £32259 cost of haemodialysis for a single patient.23 This persuasive business case, together with a sense of local ownership and the ability to incorporate eGFR graph reporting into laboratory workflows were critical in sustaining the intervention, an outcome infrequently seen in improvement work.24

The lack of impact on the primary outcome measure may reflect the complex causality of late presentation and, by international standards, the relatively low average underlying rate. Historical data from a single UK centre indicate that although late presentation for KRT was common (23.4%), late referrals accounted for only 7.4% with 3.9% deemed to be avoidable.25 High rates of late presentation have been a quality improvement priority for many years and a decline in rates occurred in centres not exposed to the intervention. A “rising tide” phenomenon has been described,26 whereby widespread efforts to tackle problems in a healthcare system contribute to null results in service improvement interventions.

The Kidney Failure Risk Equation27 has been used to guide nephrology referral practice but is limited by missing urine albumin:creatinine ratio data.28 UK guidelines recommend referral where the five-year risk of requiring KRT is greater than 5%.29 A decline in eGFR significantly increases the predicted risk of ESKD,30 and the use of dynamic eGFR data may allow earlier opportunities to improve the management of more rapidly progressive CKD. A graph of patients’ data combines the predictive power of the trend in eGFR with the information conveyed by a visual display of variation in kidney function.31 Machine learning AI techniques may enable the automation of this surveillance by pathology laboratories.32

This study has a number of limitations. Stepped-wedge cluster randomised trials are an appropriate way to evaluate the implementation of interventions with established benefit but they only succeed when the start times can be controlled. In ASSIST-CKD, organisational level complexities prohibited controlled implementation. Whilst the lack of formal randomisation in theory limits the internal validity of the study, the timing of implementation was not under the control of clinicians and therefore randomisation was arguably unnecessary in practice to adjust for external factors that might have influenced late presentation rates. Our revised quasi-experimental design is strengthened not only by this *de facto* randomisation and the availability of data from control periods, but also through the inclusion of non-intervention sites to explore time trends. Despite the power of the study being increased by including additional sites, an inadequate sample size may have resulted in statistical non-significance. Although the completeness of the routinely collected data supplied by the UKRR was generally high the incomplete coverage of catchment populations of those kidney centres served by multiple laboratories was only partially mitigated by postcode mapping, and a significant proportion (>50%) of data informing the eGFR outcome was missing. We did not capture how many patients moved out of the study catchment area after being flagged and then commenced renal replacement at a non-trial centre. Although there is a significant competing risk of death versus renal replacement in this population, we do not have details of patients who died in follow-up after an alert. Ninety days has been the traditional definition of late presentation in the UK. However, referral within one year of starting KRT is a better standard of good practice, as recommended in current national guidance.23

In conclusion, population-based surveillance of dynamic eGFR trends is an inexpensive and acceptable intervention spanning family doctors, pathology laboratories and specialist kidney services. It has been implemented at scale, evaluated using high quality routinely-collected data, and sustained without external funding in the medium term. Although eGFR graph reporting was followed by a reduction in rates of late presentation for KRT, particularly in those centres with the highest rates, improvements over time were also seen in sites where the intervention was not implemented, and after adjustment for these secular trends there was no benefit of the intervention on late presentation over standard care.

**Disclosures**

The authors declare that they have no competing interests.

**Data Sharing**

The data for the trial is held by the UK Renal Registry. Sharing of individual participant data is not possible due to the national ethical permissions governing the operation of the UK Renal Registry (section 251, NHS Act 2006). Analyable aggregate data is available on request from the study team.

**Author Contributions**

HG: conception and design, manuscript writing and revision

SM: design, manuscript writing and revision

AC: design (statistics), manuscript writing and revision

HR: conception and design, manuscript writing and revision

EL: design (statistics), manuscript writing and revision

NT: design (qualitative), manuscript writing and revision

AD: design (laboratory), manuscript writing and revision

DK: design (laboratory), manuscript writing and revision

LW: delivery, manuscript writing and revision

MLN: conception and design, manuscript writing and revision

FC: conception and design, manuscript writing and revision

All authors approved the final manuscript

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**Abbreviations**

ASSIST-CKD A programme to Spread eGFR graph Surveillance for the early identification, Support and Treatment of people with progressive CKD (ASSIST-CKD)

BME Black and minority ethnic

CKD Chronic Kidney Disease

CONSORT Consolidated Standards of Reporting Trials

eGFR Estimated glomerular filtration rate

ESKD End-stage kidney disease

HD Haemodialysis

ISRCTN International Standard Randomised Controlled Trial Number

KRT Kidney replacement therapy

LCL Lower confidence limit

OR Odds ratio

PCP Primary Care Physician

PD Peritoneal dialysis

PRD Primary Renal Diagnosis

SE Standard error

SQL Structured query language

TIDieR Template for intervention description and replication

UK United Kingdom

UKRR UK Renal Registry

UCL Upper confidence limit

**Supplementary materials**

Supplementary Material S1. CONSORT 2010 and CONSORT-ROUTINE checklist

Supplementary Material S2. Checklist of information to include when reporting a stepped wedge cluster randomised trial

Supplementary Material S3. TIDieR checklist

Supplementary Material S4. Additional methods and results

Supplementary Material S5. Supplementary Tables

Supplementary Table S1. Late referral rates - sensitivity analyses

Supplementary Table S2a. Late presentation rates by calendar year

Supplementary Table S2b. Fall in late presentation rates per year

Supplementary Table S3. Secondary outcomes - sensitivity analyses

Supplementary Table S4. Participating laboratories and renal centres: populations served and duration of eGFR reporting

Supplementary Table S5. Results of randomisation

Supplementary Material S6. Statistical analysis plan for ASSIST-CKD, a stepped wedge cluster randomised trial

Supplementary Material S7. CKD Made Easy guide

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**Figure Legends**

Figure 1. Logic model for ASSIST-CKD. ASSIST-CKD: A programme to spread eGFR graph surveillance for the early identification, support and treatment of people with progressive chronic kidney disease, CCG: Clinical Commissioning Group. CKD: Chronic Kidney Disease, GP: General Practitioner, Labs: laboratories, QI: Quality Improvement, UK: United Kingdom. The ASSIST intervention was complex and attempted to influence behaviour across the health care system from family doctors and laboratories, through to specialist kidney services and both local and national commissioners of healthcare, with the aim of determining whether there was evidence to support implementation at a UK-wide level.

Figure 2. CONSORT diagram. Summary of recruitment, randomisation, follow up and analysis of ASSIST sites. A decision to switch to a before and after design was made in 2017. The decision to convert to a quasi-experimental design also allowed the control cohort to be extended to include patients in non-participating kidney centres with data completeness for late presentation greater than 70% for each year of the study period of the incident cohort, and the addition of four intervention sites who were participating in a parallel project using the same intervention, outcomes measures, investigators and project management team funded by the East Midlands Strategic Clinical Network.

Figure 3 . Late presentation rates over time in intervention and control sites. Rates of late presentation (expressed as a percentage of incident cases of ESKD) over time in intervention (solid line) and control (dashed line) sites. The rate of late presentation fell from 16.6% in 2013 to 13.9% in 2019 in intervention sites and from 17.7% in 2013 to 15.9% in 2019 in control sites. The number of sites implementing the intervention during each year is indicated in the bottom of the figure.

**Table 1. Baseline characteristics of cohort**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Intervention: ASSIST-CKD sites** | | | | **Control: ASSIST-CKD sites** | | | | **Control: Rest of UK** | | | |
|  | **Total** | **% All** | **% Early referral** | **% Late referral** | **Total** | **% All** | **% Early referral** | **% Late referral** | **Total** | **% All** | **% Early referral** | **% Late referral** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Total** | 2373 |  | 86.1 | 14.0 | 3727 |  | 83.7 | 16.3 | 34720 |  | 84.2 | 15.8 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Age:** |  |  |  |  |  |  |  |  |  |  |  |  |
| <60 | 900 | 37.9 | 37.6 | 40.2 | 1380 | 37.0 | 37.2 | 36.4 | 13972 | 40.2 | 40.0 | 41.7 |
| 60-75 | 855 | 36.0 | 36.3 | 34.4 | 1351 | 36.3 | 36.4 | 35.8 | 12529 | 36.1 | 36.2 | 35.5 |
| >75 | 618 | 26.0 | 26.2 | 25.4 | 996 | 26.7 | 26.5 | 27.8 | 8219 | 23.7 | 23.8 | 22.8 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Sex:** |  |  |  |  |  |  |  |  |  |  |  |  |
| Male | 1445 | 60.9 | 60.7 | 61.9 | 2351 | 63.1 | 62.5 | 66.2 | 22029 | 63.5 | 63.1 | 65.2 |
| Female | 928 | 39.1 | 39.3 | 38.1 | 1376 | 36.9 | 37.5 | 33.8 | 12691 | 36.6 | 36.9 | 34.8 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Deprivation** |  |  |  |  |  |  |  |  |  |  |  |  |
| 1-least | 306 | 12.9 | 12.6 | 14.5 | 502 | 13.5 | 13.3 | 14.2 | 5346 | 15.4 | 15.7 | 14.1 |
| 2 | 377 | 15.9 | 16.0 | 15.4 | 672 | 18.0 | 18.0 | 18.5 | 6162 | 17.8 | 17.7 | 18.4 |
| 3 | 439 | 18.5 | 18.4 | 19.0 | 728 | 19.5 | 19.5 | 19.9 | 6923 | 20.0 | 20.1 | 19.5 |
| 4 | 623 | 26.3 | 26.3 | 26.0 | 866 | 23.2 | 23.5 | 21.8 | 7735 | 22.3 | 22.1 | 23.6 |
| 5-most | 628 | 26.5 | 26.7 | 25.1 | 959 | 25.7 | 25.7 | 25.7 | 8523 | 24.6 | 24.6 | 24.5 |
| Missing | 0 |  |  |  | 0 |  |  |  | 31 | 0.1 | 0.1 | 0.2 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Ethnicity** |  |  |  |  |  |  |  |  |  |  |  |  |
| BME | 243 | 10.6 | 10.4 | 11.7 | 396 | 10.8 | 11.5 | 7.6 | 7173 | 23.2 | 23.8 | 20.2 |
| White | 2054 | 89.4 | 89.6 | 88.3 | 3256 | 89.2 | 88.5 | 92.4 | 23724 | 76.8 | 76.2 | 79.8 |
| Missing | 76 | 3.2 | 2.6 | 7.3 | 75 | 2.0 | 1.9 | 2.5 | 3823 | 11.0 | 10.9 | 11.9 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **PRD** |  |  |  |  |  |  |  |  |  |  |  |  |
| Diabetic | 648 | 29.2 | 31.5 | 13.6 | 935 | 25.9 | 28.8 | 10.4 | 9500 | 28.4 | 30.9 | 14.8 |
| Non-Diabetic | 1569 | 70.8 | 68.5 | 86.4 | 2673 | 74.1 | 71.2 | 89.6 | 23950 | 71.6 | 69.1 | 85.2 |
| Missing | 156 | 6.6 | 5.1 | 15.4 | 119 | 3.2 | 2.5 | 6.8 | 1270 | 3.7 | 3.2 | 6.2 |

Table 1 legend. Baseline characteristics of cohort. Data (including missing data) are presented for age, sex, index of multiple deprivation, ethnicity (black and minority ethnic [BME], white) and primary renal diagnosis [PRD] (diabetic renal disease and non-diabetic renal disease) of incident kidney replacement therapy (KRT) patients at ASSIST-CKD sites (during intervention and control periods) and the rest of the UK.

**Table 2. Rates of late presentation in ASSIST-CKD sites (during control and intervention periods) and the rest of the United Kingdom**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **% Late presentation** | | | **Model-1** | | | | **Primary outcome. Model-2** | | | | **Model-3** | | | |
|  |  |  | **(treatment effect)** | | | | **(treatment effect, adjusted for time)** | | | | **(treatment effect, adjusted for time & covariates)** | | | |
| **Intervention: ASSIST-CKD sites** | **Control: ASSIST-CKD sites** | **Control: rest of UK** | **OR** | **LCL** | **UCL** | ***P*-value** | **OR** | **LCL** | **UCL** | ***P*-value** | **OR** | **LCL** | **UCL** | ***P*-value** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 14.0 | 16.3 | 15.8 | 0.85 | 0.74 | 0.98 | 0.02 | 0.9 | 0.78 | 1.05 | 0.18 | 0.91 | 0.78 | 1.06 | 0.23 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

Table 2 legend. Percentage of incident kidney replacement therapy (KRT) patients first seen in a renal centre less than 90 days before the commencement of KRT. Data are presented for ASSIST-CKD sites during intervention and control periods and for the rest of the UK. OR (odds ratios) and 95% confidence intervals (LCL, lower confidence limit; UCL, upper confidence limit) for late presentation with exposure to the ASSIST-CKD intervention (treatment effect) are reported for unadjusted data with centre fitted as a random effect, for data adjusted for calendar time (primary outcome measure) and for data adjusted for calendar time and individual patient characteristics (age at start of KRT, gender, PRD [primary renal diagnosis], ethnicity and index of multiple deprivation quintile).

**Table 3. Rates of late presentation (during control and intervention periods) for each intervention site**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Laboratory** | **Renal unit** | **Graphs reported per 10000 population per month** | **Number of new KRT cases in control period\*** | **Number of new KRT cases in intervention period**\* | **Number of new KRT cases in control plus intervention periods\*** | **% Late presentation adjusted for calendar time (Model-2)** | | **Change in % late presentation rate (intervention – control)** |
|  | **Control period** | **Intervention period** |
| Chester | Wirral | 3.1 | 57 | 57 | 114 | 30.3 | 14.2 | -16.1 |
| Northampton | Leicester | 6.2 | 150 | 72 | 222 | 28.7 | 20.5 | -8.2 |
| Southport | Liverpool Aintree | 10.8 | 81 | 63 | 144 | 26.2 | 18.1 | -8.1 |
| Doncaster | Doncaster | 11.4 | 118 | 184 | 302 | 21.0 | 11.1 | -9.9 |
| Hywel | Swansea | 4.9 | 321 | 75 | 396 | 20.3 | 8.5 | -11.8 |
| Truro | Truro | 16.7 | 116 | 244 | 360 | 19.0 | 15.5 | -3.4 |
| Hull | Hull | 3.5 | 241 | 94 | 335 | 18.8 | 24.7 | 5.9 |
| Wirral | Wirral | 7.1 | 96 | 109 | 205 | 17.9 | 15.9 | -2.1 |
| Southport | Liverpool Royal | 10.8 | 124 | 93 | 217 | 17.2 | 22.3 | 5.1 |
| Swansea | Swansea | 4.7 | 342 | 169 | 511 | 14.9 | 9.3 | -5.6 |
| Antrim | Antrim | 1.7 | 201 | 75 | 276 | 14.2 | 15.4 | 1.2 |
| Sherwood forest | Nottingham | 8.0 | 104 | 45 | 149 | 14.1 | 11.7 | -2.4 |
| Derby | Derby | not available | 269 | 59 | 328 | 14.0 | 16.2 | 2.2 |
| Newry | Newry | 2.7 | 83 | 105 | 188 | 13.9 | 23.6 | 9.7 |
| Leicester | Leicester | 2.6 | 441 | 260 | 701 | 13.1 | 12.5 | -0.5 |
| Wrexham | Wrexham | 8.2 | 158 | 30 | 188 | 13.1 | 3.5 | -9.5 |
| Monklands | Monklands | 12.6 | 141 | 241 | 382 | 12.2 | 9.3 | -2.9 |
| Kettering | Leicester | 9.4 | 120 | 126 | 246 | 12.1 | 14.0 | 1.9 |
| Sunderland | Sunderland | 3.7 | 238 | 113 | 351 | 12.0 | 14.0 | 2.0 |
| Epsom & St Helier | Carshalton | 7.0 | 140 | 102 | 242 | 10.4 | 17.3 | 6.9 |
| Derry | Derry | 10.4 | 186 | 57 | 243 | 10.1 | 16.7 | 6.6 |

Table 3 legend. Late presentation rates and graph reporting rates at individual sites in descending order of late presentation rate during control period. Data are presented for the numbers of graphs reported to Primary Care expressed as a rate per 10000 population served per month and the number and percentage (adjusted for calendar time) of incident kidney replacement therapy (KRT) patients first seen in each unit less than 90 days before the commencement of KRT during control and intervention periods. \* Data completeness was over 95% for all centres, excluding Scottish data (from Monklands) missing from the second half of 2019.

**Table 4. Secondary outcomes**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Intervention: ASSIST-CKD sites** | **Control: ASSIST-CKD sites** | **Control: rest of UK** | **Model-1 (treatment only)** | | | | **Model-2 (treatment, adjusted for time)** | | | | **Model-3 (treatment, adjusted for time and covariates)** | | | |
|  | **% with permanent access** | | | **OR** | **LCL** | **UCL** | ***P*-value** | **OR** | **LCL** | **UCL** | ***P*-value** | **OR** | **LCL** | **UCL** | ***P*-value** |
| **Permanent access in all people receiving KRT** | 56.8 | 58.9 | 57.0 | 0.99 | 0.88 | 1.11 | 0.83 | 0.99 | 0.88 | 1.11 | 0.81 | 0.99 | 0.88 | 1.11 | 0.83 |
| **Permanent access in all patients receiving haemodialysis** | 43.3 | 43.9 | 39.3 | 1.01 | 0.89 | 1.15 | 0.87 | 1.05 | 0.91 | 1.2 | 0.52 | 1.05 | 0.91 | 1.2 | 0.53 |
|  | **% died by 6 months** | | | **OR to be alive at 6 months after start of KRT** | | | | | | | | | | | |
| **Mortality at 6 months** | 9.8 | 9.3 | 8.1 | 0.95 | 0.8 | 1.12 | 0.55 | 0.92 | 0.77 | 1.1 | 0.18 | 0.91 | 0.76 | 1.1 | 0.33 |
|  |  |  |  | **Estimate change in eGFR pre-RRT start** | | | | | | | | | | | |
|  | **mean (standard deviation)** | | | **estimate** | **SE** |  | ***P*-value** | **estimate** | **SE** |  | ***P*-value** | **estimate** | **SE** |  | ***P*-value** |
| **eGFR pre-RRT start** | 9.0 (2.9) | 9.0 (3.0) | 9.1 (3.3) | 0.17 | 0.12 |  | 0.16 | 0.27 | 0.13 |  | 0.04 | 0.23 | 0.13 |  | 0.08 |

Table 4 legend. Secondary outcomes: percentage of incident kidney replacement therapy (KRT) patients receiving KRT via permanent access; percentage of incident KRT patients receiving haemodialysis via permanent access; 6-month mortality in incident KRT patients; eGFR at KRT start. Data are presented for ASSIST-CKD sites during control and intervention periods and for the rest of the UK, and analysed by intervention time period. For percentage of KRT patients receiving KRT via permanent access, percentage of incident KRT patients receiving haemodialysis via permanent access and percentage of incident KRT died by 6 months, OR (odds ratios) and 95% confidence intervals (LCL, lower confidence limit; UCL, upper confidence limit) with exposure to the ASSIST-CKD intervention (treatment effect) are reported for unadjusted data with centre fitted as a random effect, for data adjusted for calendar time, and for data adjusted for calendar time and individual patient characteristics (age at start of KRT, gender, primary renal diagnosis [PRD], ethnicity and index of multiple deprivation quintile). For eGFR pre-KRT start data are presented as means and standard deviations, with the estimated change in eGFR for each Model provided as a point estimate and standard error (SE).

Box 1. Summary of the study in Population Intervention Comparison Outcome (PICO) Format

|  |
| --- |
| **Population** – All adults in Primary Care in participating regions.  **Intervention** – A multi-component complex intervention: (1) graphical presentation of patients’ eGFR results from routine blood tests; (2) review of all graphs by trained laboratory or kidney staff; and (3) reporting of selected graphs to Primary Care. The threshold for generating graphs was last eGFR <50 ml/min/1.73 m2 for patients aged 18-65 and <40 ml/min/1.73 m2 for patients aged >65 years.  **Comparison** – Standard of care.  **Outcome** – Late presentation for KRT, defined as less than 90 days between first nephrology clinic visit and first start of KRT. |

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