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Volume 9 • Issue 10 • August 2021

ISSN 2050-4322

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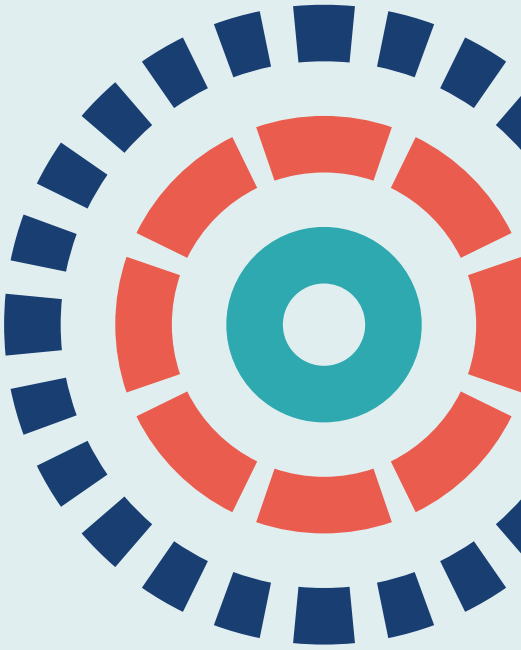

DOI 10.3310/pgfar09100

Long-term monitoring in primary care for chronic kidney disease and chronic heart failure: a multi-method research programme

Rafael Perera,[1*] Richard Stevens,[1] Jeffrey K Aronson,[1] Amitava Banerjee,[2] Julie Evans,[1] Benjamin G Feakins,[1] Susannah Fleming,[1] Paul Glasziou,[3] Carl Heneghan,[1] FD Richard Hobbs,[1] Louise Jones,[1] Milena Kurtinecz,[1] Daniel S Lasserson,[4] Louise Locock,[5] Julie McLellan,[1] Borislava Mihaylova,[6,7] Christopher A O'Callaghan,[8] Jason L Oke,[1] Nicola Pidduck,[1] Annette Plüddemann,[1] Nia Roberts,[9] Iryna Schlackow,[6] Brian Shine,[10] Claire L Simons,[6] Clare J Taylor,[1] Kathryn S Taylor,[1] Jan Y Verbakel[1,11,12] and Clare Bankhead[1]

[1]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[2]Institute of Health Informatics, University College London, London, UK
[3]Institute for Evidence-Based Healthcare, Faculty of Health Sciences & Medicine, Bond University, Gold Coast, QLD, Australia
[4]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
[5]Health Services Research Unit, University of Aberdeen, Aberdeen, UK
[6]Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[7]Institute of Population Health Sciences, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[8]Nuffield Department of Medicine, University of Oxford, Oxford, UK
[9]Bodleian Health Care Libraries, Knowledge Centre, University of Oxford, Oxford, UK
[10]Department of Clinical Biochemistry, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[11]Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium
[12]National Institute for Health Research (NIHR) Community Healthcare MedTech and In Vitro Diagnostics Co-operative (MIC), Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

*Corresponding author

Declared competing interests of authors: Rafael Perera reports grants from the National Institute for Health Research (NIHR) Programme Grants for Applied Research programme [RP-PG-1210-12012: the early use of Antibiotics for at Risk CHildren with InfluEnza in primary care (the ARCHIE programme)], the British Heart Foundation (PG/17/49/33099), the NIHR School for Primary Care Research (Wittenberg_FR16), the NIHR Oxford Biomedical Research Centre (BRC) (IS-BRC-1215-20008) and the NIHR Community Healthcare MedTech and In Vitro Diagnostics Co-operative (MIC-2016-018) during the conduct of the study. Jeffrey K Aronson has co-authored and edited textbooks and written reviews, commentaries and medicolegal reports on various aspects of prescribing. He has provided expert reports on cases involving adverse drug reactions, most often for coroners, sometimes on behalf of private individuals, and occasionally for pharmaceutical companies. He was previously a member of the NIHR Journals Library Board from 2012 until it was disbanded. Amitava Banerjee reports personal fees from C.H. Boehringer Sohn AG & Ko. KG (Ingelheim am Rhein,, Germany), AstraZeneca plc (Cambridge, UK), Novo Nordisk A/S (Bagsværd, Denmark) and Pfizer Inc. (New York, NY, USA) outside the submitted work, all before 2017. He is a trustee of the South Asian Health Foundation (2014–present) and was a member of the Education Committee of the British Cardiovascular Society (2017–20). Carl Heneghan reports expenses and fees for his media work and expenses from the World Health Organization; and holds grant funding from the NIHR Oxford Biomedical Research Centre and the NIHR School for Primary Care Research Evidence Synthesis Working Group (project 390). He has received financial remuneration from an asbestos case. He receives expenses for teaching evidence-based medicine and is also paid for his general practitioner work in the NHS out of hours. He is Director of the Centre for Evidence-Based Medicine at the University of Oxford, Editor in Chief of the *British Medical Journal Evidence-Based Medicine* and a NIHR Senior Investigator. FD Richard Hobbs reports grants from a NIHR Professorship (NIHR-RP-R2-12-015) during the conduct of the study; reports personal fees and other from Novartis International AG (Basel Switzerland), C.H. Boehringer Sohn AG & Ko. KG; and reports grants from Pfizer Inc. outside the submitted work. Milena Kurtinecz is a GlaxoSmithKline plc (Brentford, UK) employee and owns company stock. GlaxoSmithKline plc provided access to limited placebo data for some analyses. Louise Locock reports membership of the NIHR Health Services and Delivery Research board during the lifetime of the study (2014–19). Julie McLellan reports occasional expenses for teaching evidence-based medicine. Borislava Mihaylova reports grants from Merck & Co. Inc. (Kenilworth, NJ, USA) outside the submitted work and support from the NIHR Oxford Biomedical Research Centre (IS-BRC-1215-20008) and NIHR HTA (17/140/02). Christopher A O'Callaghan receives standard academic grants from the Novo Nordisk Foundation (NNF15SA0018346), the Medical Research Council (MC_PC_17174), the European Foundation for the Study of Diabetes (grant 96111) and Diabetes Research UK (15/0005171). Annette Plüddemann reports grant funding from the NIHR School for Primary Care Research (SPCR) (NIHR SPCR Evidence Synthesis Working Group project 390) during the conduct of the study, and occasionally receives expenses for teaching evidence-based medicine. Clare J Taylor reports personal fees from Novartis International AG and Vifor Pharma (Glattbrugg, Switzerland), and non-financial support from F. Hoffman-La Roche Ltd (Basel, Switzerland) outside the submitted work. Clare Bankhead reports grants from Cancer Research UK (EDAG committee 27880), the NIHR Oxford BRC (Multimorbidity theme IS-BRC-1215-20008) and the NIHR School for Primary Care Research (Wittenberg_FR16) during the conduct of the study.

Published August 2021
DOI: 10.3310/pgfar09100

This report should be referenced as follows:

Perera R, Stevens R, Aronson JK, Banerjee A, Evans J, Feakins BG, *et al*. Long-term monitoring in primary care for chronic kidney disease and chronic heart failure: a multi-method research programme. *Programme Grants Appl Res* 2021;**9**(10).

Programme Grants for Applied Research

ISSN 2050-4322 (Print)

ISSN 2050-4330 (Online)

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Editorial contact: journals.library@nihr.ac.uk

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This report

The research reported in this issue of the journal was funded by PGfAR as project number RP-PG-1210-12003. The contractual start date was in January 2014. The final report began editorial review in September 2019 and was accepted for publication in September 2020. As the funder, the PGfAR programme agreed the research questions and study designs in advance with the investigators. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The PGfAR editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, CCF, NETSCC, PGfAR or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the PGfAR programme or the Department of Health and Social Care.

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Abstract

Long-term monitoring in primary care for chronic kidney disease and chronic heart failure: a multi-method research programme

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[1]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[2]Institute of Health Informatics, University College London, London, UK
[3]Institute for Evidence-Based Healthcare, Faculty of Health Sciences & Medicine, Bond University, Gold Coast, QLD, Australia
[4]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
[5]Health Services Research Unit, University of Aberdeen, Aberdeen, UK
[6]Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[7]Institute of Population Health Sciences, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[8]Nuffield Department of Medicine, University of Oxford, Oxford, UK
[9]Bodleian Health Care Libraries, Knowledge Centre, University of Oxford, Oxford, UK
[10]Department of Clinical Biochemistry, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[11]Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium
[12]National Institute for Health Research (NIHR) Community Healthcare MedTech and In Vitro Diagnostics Co-operative (MIC), Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

*Corresponding author Rafael.perera@phc.ox.ac.uk

Background: Long-term monitoring is important in chronic condition management. Despite considerable costs of monitoring, there is no or poor evidence on how, what and when to monitor. The aim of this study was to improve understanding, methods, evidence base and practice of clinical monitoring in primary care, focusing on two areas: chronic kidney disease and chronic heart failure.

Objectives: The research questions were as follows: does the choice of test affect better care while being affordable to the NHS? Can the number of tests used to manage individuals with early-stage kidney disease, and hence the costs, be reduced? Is it possible to monitor heart failure using a simple blood test? Can this be done using a rapid test in a general practitioner consultation? Would changes in the management of these conditions be acceptable to patients and carers?

Design: Various study designs were employed, including cohort, feasibility study, Clinical Practice Research Datalink analysis, seven systematic reviews, two qualitative studies, one cost-effectiveness analysis and one cost recommendation.

Setting: This study was set in UK primary care.

Data sources: Data were collected from study participants and sourced from UK general practice and hospital electronic health records, and worldwide literature.

Participants: The participants were NHS patients (Clinical Practice Research Datalink: 4.5 million patients), chronic kidney disease and chronic heart failure patients managed in primary care (including 750 participants in the cohort study) and primary care health professionals.

Interventions: The interventions were monitoring with blood and urine tests (for chronic kidney disease) and monitoring with blood tests and weight measurement (for chronic heart failure).

Main outcome measures: The main outcomes were the frequency, accuracy, utility, acceptability, costs and cost-effectiveness of monitoring.

Results: Chronic kidney disease: serum creatinine testing has increased steadily since 1997, with most results being normal (83% in 2013). Increases in tests of creatinine and proteinuria correspond to their introduction as indicators in the Quality and Outcomes Framework. The Chronic Kidney Disease Epidemiology Collaboration equation had 2.7% greater accuracy (95% confidence interval 1.6% to 3.8%) than the Modification of Diet in Renal Disease equation for estimating glomerular filtration rate. Estimated annual transition rates to the next chronic kidney disease stage are $\approx$ 2% for people with normal urine albumin, 3–5% for people with microalbuminuria (3–30 mg/mmol) and 3–12% for people with macroalbuminuria (> 30 mg/mmol). Variability in estimated glomerular filtration rate-creatinine leads to misclassification of chronic kidney disease stage in 12–15% of tests in primary care. Glycaemic-control and lipid-modifying drugs are associated with a 6% (95% confidence interval 2% to 10%) and 4% (95% confidence interval 0% to 8%) improvement in renal function, respectively. Neither estimated glomerular filtration rate-creatinine nor estimated glomerular filtration rate-Cystatin C have utility in predicting rate of kidney function change. Patients viewed phrases such as 'kidney damage' or 'kidney failure' as frightening, and the term 'chronic' was misinterpreted as serious. Diagnosis of asymptomatic conditions (chronic kidney disease) was difficult to understand, and primary care professionals often did not use 'chronic kidney disease' when managing patients at early stages. General practitioners relied on Clinical Commissioning Group or Quality and Outcomes Framework alerts rather than National Institute for Health and Care Excellence guidance for information. Cost-effectiveness modelling did not demonstrate a tangible benefit of monitoring kidney function to guide preventative treatments, except for individuals with an estimated glomerular filtration rate of 60–90 ml/minute/1.73 m^2, aged < 70 years and without cardiovascular disease, where monitoring every 3–4 years to guide cardiovascular prevention may be cost-effective. Chronic heart failure: natriuretic peptide-guided treatment could reduce all-cause mortality by 13% and heart failure admission by 20%. Implementing natriuretic peptide-guided treatment is likely to require predefined protocols, stringent natriuretic peptide targets, relative targets and being located in a specialist heart failure setting. Remote monitoring can reduce all-cause mortality and heart failure hospitalisation, and could improve quality of life. Diagnostic accuracy of point-of-care N-terminal prohormone of B-type natriuretic peptide (sensitivity, 0.99; specificity, 0.60) was better than point-of-care B-type natriuretic peptide (sensitivity, 0.95; specificity, 0.57). Within-person variation estimates for B-type natriuretic peptide and weight were as follows: coefficient of variation, 46% and coefficient of variation, 1.2%, respectively. Point-of-care N-terminal prohormone of B-type natriuretic peptide within-person variability over 12 months was 881 pg/ml (95% confidence interval 380 to 1382 pg/ml), whereas

between-person variability was 1972 pg/ml (95% confidence interval 1525 to 2791 pg/ml). For individuals, monitoring provided reassurance; future changes, such as increased testing, would be acceptable. Point-of-care testing in general practice surgeries was perceived positively, reducing waiting time and anxiety. Community heart failure nurses had greater knowledge of National Institute for Health and Care Excellence guidance than general practitioners and practice nurses. Health-care professionals believed that the cost of natriuretic peptide tests in routine monitoring would outweigh potential benefits. The review of cost-effectiveness studies suggests that natriuretic peptide-guided treatment is cost-effective in specialist settings, but with no evidence for its value in primary care settings.

Limitations: No randomised controlled trial evidence was generated. The pathways to the benefit of monitoring chronic kidney disease were unclear.

Conclusions: It is difficult to ascribe quantifiable benefits to monitoring chronic kidney disease, because monitoring is unlikely to change treatment, especially in chronic kidney disease stages G3 and G4. New approaches to monitoring chronic heart failure, such as point-of-care natriuretic peptide tests in general practice, show promise if high within-test variability can be overcome.

Future work: The following future work is recommended: improve general practitioner–patient communication of early-stage renal function decline, and identify strategies to reduce the variability of natriuretic peptide.

Study registration: This study is registered as PROSPERO CRD42015017501, CRD42019134922 and CRD42016046902.

Funding: This project was funded by the National Institute for Health Research (NIHR) Programme Grants for Applied Research programme and will be published in full in *Programme Grants for Applied Research*; Vol. 9, No. 10. See the NIHR Journals Library website for further project information.

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ACE	angiotensin-converting enzyme
ACR	albumin–creatinine ratio
ARB	angiotensin receptor blocker
b.i.d.	bis in die
BNP	B-type natriuretic peptide
CHF	chronic heart failure
CHFN	community heart failure nurse
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CPRD	Clinical Practice Research Datalink
CV	coefficient of variation
CVD	cardiovascular disease
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
ESRD	end-stage renal disease
FORM-2C	Frequency Of Renal Monitoring – Creatinine and Cystatin C
GFR	glomerular filtration rate
GP	general practitioner
GUIDE-IT	Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure
HbA_{1c}	glycated haemoglobin
HERG	Health Experiences Research Group
KDIGO	Kidney Disease: Improving Global Outcomes
LDL	low-density lipoprotein
LVEF	left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
mGFR	measured glomerular filtration rate
NDPCHS	Nuffield Department of Primary Care Health Sciences
NICE	National Institute for Health and Care Excellence
NP	natriuretic peptide
NSAID	non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
NYHA	New York Heart Association
PDA	personal digital assistant
PI	principal investigator
POC	point of care
PPI	patient and public involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life-year
QOF	Quality and Outcomes Framework
RCT	randomised controlled trial
RCV	reference change value
RM	remote monitoring
RR	risk ratio
RRT	renal replacement therapy
SE	standard error
SMD	standardised mean difference
STS	structured telephone support
TM	telemonitoring
WS	workstream

Plain English summary

In the UK, long-term (chronic) conditions such as diabetes, high blood pressure and many others are often monitored and managed by general practitioners. It can be difficult for the NHS to decide how frequently a long-term condition should be monitored; more frequent monitoring is not always more useful. We studied chronic kidney disease and chronic heart failure. To complement our previous work on kidney disease in diabetes, we emphasise other kidney disease in this study.

For managing chronic kidney disease, we found that the number of tests used in the NHS has vastly increased, but, for most patients, the tests are unlikely to influence treatment. There are treatments that can prevent kidney disease getting worse, but they are usually treatments that most of the patients are already likely to be prescribed for other reasons (e.g. high levels of cholesterol or diabetes). When we combined estimates of the accuracy of the tests with this information about treatment options, we found that, among people with chronic kidney disease, it is hard to demonstrate benefits of annual monitoring that would be worth the health-care costs or the patients' time. We also found that patients can misunderstand the term 'chronic kidney disease'; for example, they may associate it with dialysis, kidney transplants and kidney failure, whereas these serious outcomes apply to only a very small number of people with late-stage chronic kidney disease.

Chronic heart failure, however, is always a serious condition urgently requiring careful treatment (e.g. blood pressure-lowering drugs). Monitoring is essential to prescribe appropriate treatment for each patient. At present, monitoring takes the form of regular check-ups (on blood pressure, weight, etc.). Previous trials have found that blood tests called natriuretic peptide tests, usually carried out at a hospital or a laboratory, could make monitoring more effective, and so improve patient health. We found that installing natriuretic peptide testing devices at general practice surgeries would be feasible, but the accuracy of these devices needs to be improved.

Scientific summary

Background

As life expectancy improves, more people are living with chronic conditions, many of which are managed in primary care. Earlier diagnoses also shift the burden of disease management towards primary care. Monitoring is an established, and often incentivised, component of the management of long-term conditions, but the evidence base for monitoring, and details of a monitoring strategy (e.g. frequency), is sparse. It has been shown previously that more frequent monitoring is not necessarily better for health.

Objectives

We aimed to improve understanding, methods, the evidence base and the practice of clinical monitoring in UK primary care, using two exemplar chronic diseases managed in primary care: chronic kidney disease and chronic heart failure.

For chronic kidney disease, the aims were to describe current monitoring practice, including national variations and time trends; summarise evidence comparing different equations for deriving estimated glomerular filtration rate from serum creatinine; study the accuracy of diagnosed chronic kidney disease stages based on estimated glomerular filtration rate; identify pharmacological interventions that delay progression of chronic kidney disease; assess how outcomes vary with frequency of monitoring; compare the predictive power of current (serum creatinine) and novel (cystatin C) biomarkers for calculating estimated glomerular filtration rate; investigate patients' and health professionals' attitudes to and experiences of monitoring; and estimate the cost-effectiveness of monitoring more or less frequently.

For chronic heart failure, the aims were to assess whether or not natriuretic peptide-guided treatment improves outcomes; identify individual components of the interventions that lead to these improvements; evaluate the effectiveness of remote monitoring from home; review evidence of the diagnostic accuracy of point-of-care devices in primary care; estimate the variability of natriuretic peptide and weight measurement; investigate the feasibility of using point-of-care natriuretic peptide testing devices in the monitoring of chronic heart failure; understand patient and health professional views and experiences of monitoring chronic heart failure; and investigate the health economic issues of chronic heart failure monitoring.

Methods and results

Chronic kidney disease

We used a database of laboratory tests in Oxfordshire and a national database (the Clinical Practice Research Datalink) to study trends and variation in monitoring of kidney disease with blood and urine tests. The local data allowed us to study long-term trends over two decades across primary and secondary care. The Clinical Practice Research Datalink data allowed us to focus on primary care testing and to observe national variations in practice. In Oxfordshire, we found a steady increase from 1997 in serum creatinine testing, with the proportion of these corresponding to normal kidney function increasing from 59% to 83% between 1993 and 2013. Nationally, rates of kidney function testing increased over time in all age groups. Testing of serum creatinine levels increased rapidly between 2006 and 2007,

and testing of proteinuria increased rapidly between 2009 and 2010, dates that correspond to the introduction of relevant indicators to the Quality and Outcomes Framework.

We systematically searched literature databases for studies comparing estimated glomerular filtration rates calculated from serum creatinine using equations from the Modification of Diet in Renal Disease study or the Chronic Kidney Disease Epidemiology Collaboration with measured glomerular filtration rates in adult populations, and pooled data from 48 studies of 26,875 patients. The mean accuracy (i.e. the percentage of observations with an estimated glomerular filtration rate within 30% of the measured glomerular filtration rate) for the Chronic Kidney Disease Epidemiology Collaboration equation was 2.7% higher (95% confidence interval 1.6% to 3.8%) than for the Modification of Diet in Renal Disease equation, but with medium/large heterogeneity ($I^2 = 56\%$).

We used data from 1,973,068 adults in 643 general practices between 2005 and 2014 to fit a hidden Markov model for chronic kidney disease stage stratified by proteinuria status. This approach distinguishes true change in disease from apparent changes due to measurement error. The rate per year of true transition from one chronic kidney disease stage to the next was approximately 2% for people with normal urine albumin levels, between 3% and 5% for people with microalbuminuria (3–30 mg/mmol) and between 3% and 12% for people with macroalbuminuria (> 30 mg/mmol). We estimate misclassification of chronic kidney disease stage due to measurement variability in estimated glomerular filtration rate to occur in between 12% and 15% of all tests in primary care.

We systematically searched literature databases for randomised controlled trials of sodium bicarbonate or antihypertensive, lipid-modifying or glycaemic-control drugs in adults with chronic kidney disease followed up for at least 2 years. The primary outcome was renal function measured by measured glomerular filtration rate, estimated glomerular filtration rate, creatinine clearance or estimated creatinine clearance. In 35 studies of > 51,000 patients, we found that lipid-modifying drugs and (in diabetes) glycaemic-control drugs were associated with better renal function. No evidence of benefit of sodium bicarbonate (only two trials) or antihypertensive drugs was found.

We recruited 750 adults with chronic kidney disease in 14 general practices in the Thames Valley, to investigate whether baseline renal function measured by cystatin C or measured by serum creatinine is better at predicting change in renal function. Blood samples were taken at baseline (0, 2 and 12 weeks), at 6 months and at 6-monthly intervals for a further 18 months. The estimated glomerular filtration rate was calculated for all time points using these two biomarkers. For this report, we include 745 participants in a complete-case analysis, including patients with at least one baseline result for both creatinine and cystatin C, and at least two results for both creatinine and cystatin C from visits between 6 and 24 months. The *c*-statistic for baseline estimated glomerular filtration rate using creatinine as a predictor of future change in estimated glomerular filtration rate using creatinine was 0.495 (95% confidence interval 0.471 to 0.521). The *c*-statistic for baseline estimated glomerular filtration rate using cystatin C as a predictor of future change in estimated glomerular filtration rate using cystatin C was 0.500 (95% confidence interval 0.474 to 0.525).

Forty-five people with chronic kidney disease were interviewed, and 16 health professionals participated in four focus groups. Patient interviews revealed that phrases such as ‘kidney damage’ or ‘kidney failure’ could be frightening, and the term ‘chronic’ was sometimes misinterpreted as meaning ‘serious’. The diagnosis of an asymptomatic condition such as chronic kidney disease was reported as difficult to understand. To avoid unnecessary anxiety, primary care professionals often did not use the term ‘chronic kidney disease’ when talking to patients with early-stage kidney impairment. Patients could be concerned and wanted to know more about possible causes, the meaning of test results and preventative actions to reduce further decline.

The general practitioners relied on Clinical Commissioning Group or Quality and Outcomes Framework alerts for patient management recommendations, rather than National Institute for Health Care and

Excellence guidance. Regarding current chronic kidney disease guidelines specifically, there was confusion about when and how albumin–creatinine ratio tests should be used.

We incorporated our findings into a model of the cost-effectiveness of frequencies of monitoring chronic kidney disease in primary care. We assessed 'no monitoring', monitoring every 5, 4, 3 and 2 years and annual monitoring. Clinicians and stakeholders advised that a key objective of estimated glomerular filtration rate monitoring in primary care is guiding treatments to reduce cardiovascular risk among people with reduced kidney function. Based on the review of interventions and current guidelines, we assumed that monitoring would guide treatment with 20 mg of atorvastatin (Lipitor®, Pfizer Inc., New York, NY, USA) daily for people without prior cardiovascular disease and/or chronic kidney disease and 80 mg of atorvastatin daily for all others, with treatment with 10 mg ramipril (Tritace®, Sanofi, Paris, France) daily for people with chronic kidney disease. Under these assumptions, monitoring had little or no effect on predicted health outcomes for people with chronic kidney disease because the majority of people indicated for statin and blood pressure-lowering treatments as a result of progression of chronic kidney disease would already be indicated for the same treatment because of cardiovascular risk.

Chronic heart failure

We updated a systematic review to assess whether or not treatment guided by serial B-type natriuretic peptide or N-terminal prohormone of B-type natriuretic peptide (collectively called 'natriuretic peptide') monitoring improves outcomes, compared with treatment guided by clinical assessment alone. The updated evidence, from 19 trials, indicates that natriuretic peptide-guided treatment can reduce all-cause mortality by 13% and heart failure admission by 20%.

We identified common features of the most successful of these trials: predefined treatment protocols, setting stringent natriuretic peptide targets, incorporating relative targets and location in specialist heart failure settings. We recommend that future reviews should combine individual participant data to control for patient-level differences.

We conducted a systematic review of the clinical effectiveness of remote monitoring (telemonitoring and/or structured telephone support) for adults with heart failure. A meta-analysis of 53 studies showed statistically significant reductions in some (all-cause mortality, heart failure hospital admission), but not all, outcomes with either telemonitoring or structured telephone support.

We conducted a systematic review of point-of-care natriuretic peptide diagnostic accuracy studies. Of 37 eligible studies, five were conducted solely in primary care. The types of patients, the health-care settings and the thresholds used varied across studies. For the B-type natriuretic peptide test, in populations with low chronic heart failure prevalence, pooled sensitivity and specificity were 0.95 (95% confidence interval 0.91 to 0.97) and 0.57 (95% confidence interval 0.43 to 0.70), respectively, whereas, for N-terminal prohormone of B-type natriuretic peptide, pooled sensitivity and specificity were 0.99 (95% confidence interval 0.57 to 1.00) and 0.60 (95% confidence interval 0.44 to 0.74), respectively. Note that sensitivity varies in the primary care studies.

We estimated variability in B-type natriuretic peptide concentrations and weight in patients with heart failure in the control arm ($n = 30$) of a 13-week randomised controlled trial among patients with stable New York Heart Association class II to III chronic heart failure. The between-person coefficient of variation of weight was 26% and of B-type natriuretic peptide was 137%. Between-person variation in B-type natriuretic peptide varied with age (coefficient of variation: 170% for those aged < 55 years, 88% for those aged ≥ 55 years), but not obesity. Within-person variation was substantial, but smaller than between-person variation (coefficient of variation: 46% for B-type natriuretic peptide, 1.2% for weight). This suggests that monitoring over 3 months is unlikely to detect true B-type natriuretic peptide change against background noise in this small, stable heart failure, sample.

To assess the feasibility of point-of-care natriuretic peptide measurement in primary care, we recruited 27 adults with a confirmed heart failure. Participants attended visits at 0, 6 and 12 months. At each visit, venous blood samples were taken for point-of-care N-terminal prohormone of B-type natriuretic peptide measurement, laboratory N-terminal prohormone of B-type natriuretic peptide and renal function testing. Testing was successfully carried out at 100% of planned study visits. Within-person variability in point-of-care N-terminal prohormone of B-type natriuretic peptide over 12 months was 881 pg/ml (95% confidence interval 380 to 1382 pg/ml). Between-person variability in point-of-care N-terminal prohormone of B-type natriuretic peptide over 12 months was 1972 pg/ml (95% confidence interval 1525 to 2791 pg/ml). Between-person variability in point-of-care N-terminal prohormone of B-type natriuretic peptide was around twice as large as within-person variability over 12 months, indicating that deviations from individual set points for N-terminal prohormone of B-type natriuretic peptide are likely to be more helpful than population-level thresholds.

To understand the acceptability and impact of monitoring regimes among individuals with chronic heart failure, we analysed 59 patient interviews and conducted focus groups with 16 health professionals. Current practice varies, in both primary and secondary care, including some measurement of weight and blood pressure at home, and some use of telemonitoring. Monitoring by specialist nurses was particularly valued. Monitoring provided reassurance, although guidance about when to seek help did not seem to have been given, other than for emergencies. Patients found hypothetical future changes acceptable (e.g. increased reliance on blood testing) or welcome (point-of-care testing in general practice surgeries).

Community heart failure nurses were fully informed of relevant National Institute for Health and Care Excellence guidelines and used them daily, with adjustment for patient complexity (comorbidities). General practitioners and practice nurses expressed unfamiliarity with the latest National Institute for Health and Care Excellence guidelines. Therefore, community heart failure nurses usually lead on treatment plans. General practitioners and community heart failure nurses recognise natriuretic peptide as a useful diagnostic test for chronic heart failure, but community heart failure nurses could see no benefit of measuring natriuretic peptide as part of routine monitoring, instead suggesting that changes in chronic heart failure severity would be reflected in patients' symptoms. Health-care professionals believed that financial and time costs of the test would outweigh any potential benefits.

In a systematic review, we found 40 previous health economic models addressing heart failure monitoring, management strategies and treatments in primary care. Three studied diagnosis, 11 studied management strategies and 26 studied drug interventions. Data to inform parameters in the models (disease risks, quality of life and costs) were sourced predominantly from randomised controlled trials in chronic heart failure patients in secondary care (39 out of 40 models). Therefore, the models are unlikely to be representative of the chronic heart failure population seen in contemporary primary care.

Conclusions

Laboratory monitoring of chronic kidney disease has grown dramatically over the years, but it is not obvious what treatment can be taken in response to a decline in estimated glomerular filtration rate. The treatments with proven renoprotective properties are often already indicated for other reasons, for example statins and antihypertensives for cardiovascular prevention or glucose-lowering therapies in people with diabetes. Meanwhile, the terminology of 'chronic kidney disease' can be misunderstood by patients. Hence, it is difficult to ascribe quantifiable benefits to annual monitoring of chronic kidney disease. For chronic heart failure, treatment regimens are well established, but monitoring methods less so. Natriuretic peptide testing at the point of care may be feasible in general practice, but for both natriuretic peptide testing and weight measurement, there is high measurement variability to overcome, making it premature to recommend home or point-of-care monitoring for chronic heart failure.

Research recommendations

- Determining, with high precision, the bias, and accuracy, of estimated glomerular filtration rate equations would be of high value for the NHS, to determine when (in what settings) and how (with what protocol) these equations should be used.
- Protocols to determine best practice for combining estimated glomerular filtration rate measurements might help reduce individual measurement error.
- The possible advantages of cystatin C over serum creatinine in our cohort study need to be confirmed.
- At least one alternative to the term 'chronic kidney disease' has been proposed; its potential to improve communications should be investigated.
- Closing the gap (identified in the systematic review of interventions) of evidenced interventions that specifically protect renal function would have the greatest potential to improve the cost-effectiveness of chronic kidney disease monitoring.
- Further studies of natriuretic peptide-guided treatment for chronic heart failure are needed, especially in primary care.
- New studies of remote monitoring need to be incorporated promptly into systematic reviews and should reflect any technological changes.
- A setting-appropriate threshold must be determined if point-of-care natriuretic peptide monitoring is to be incorporated into primary care pathways.

Implications for practice

Chronic kidney disease

- Laboratories could improve the accuracy of estimated glomerular filtration rate by switching to the Chronic Kidney Disease Epidemiology Collaboration equation for its calculation.
- Potential treatments that might positively affect kidney function are lipid-modifying treatment and glycaemic-control medication.
- The rate of change of kidney function in a primary care population is slow, and most apparent changes will be due to measurement noise (error) and not real change.
- The terms 'chronic' and 'disease' act as barriers in the communication between health practitioners and patients. A potential solution is the use of alternative terms such as 'kidney age'.
- Monitoring individuals with chronic kidney disease is, at present, difficult to justify by usual rationales such as treatment initiation or titration.

Chronic heart failure

- No evidence was found of natriuretic peptide use as part of a diagnostic pathway in primary care, which goes against the National Institute for Health and Care Excellence's recommendation; its use could be incentivised.
- Both natriuretic peptide and weight are highly variable measures; therefore, any change observed should be interpreted with caution.
- The use of point-of-care tests to measure natriuretic peptide in general practice is feasible, but does not lead to reductions in observed variability.
- There are substantial barriers to the implementation of natriuretic peptide-guided treatment in primary care. In particular, the perception of health practitioners, both nurses and clinicians, is that the use of natriuretic peptide measures may not be beneficial.

Study registration

This study is registered as PROSPERO CRD42015017501, CRD42019134922 and CRD42016046902.

Funding

This project was funded by the National Institute for Health Research (NIHR) Programme Grants for Applied Research programme and will be published in full in *Programme Grants for Applied Research*; Vol. 9, No. 10. See the NIHR Journals Library website for further project information.

SYNOPSIS

Background

Advances in health promotion and better prevention, detection and treatment of diseases have led to important demographic changes in the UK, with consistent increases in healthy life expectancy. Paradoxically, this also means that a greater number of people are now living longer with one or more long-term conditions, such as diabetes, kidney disease or coronary heart disease.[1,2] In the UK, the management of these conditions has shifted from secondary care to primary care, partly because of the continuity of care that primary care provides, but also because of the generalist approach used in primary care to deal with multiple, not necessarily related, conditions.[3] A major aspect of the good management of these conditions is long-term monitoring. However, despite the considerable economic cost for most of these conditions, there is no or poor evidence on the monitoring strategies used, for example how, what and when to monitor.[4]

In particular, the frequency of monitoring has received little attention. A higher frequency of monitoring does not necessarily lead to better management.[5] Besides the financial costs, there are considerable downsides to overfrequent measurement. There are personal costs, such as the time spent, the need for invasive tests, the extra levels of anxiety and sometimes unnecessary hospital visits. More directly relevant, a higher frequency of monitoring increases the potential for inadequate management based on test results showing, incorrectly, deterioration when, in reality, the observed change is due to measurement variability only.[5,6] The overall aim of this programme was to develop a better understanding, extend the methods, increase the evidence base and improve the practice of clinical monitoring in UK primary care.

As background for this programme, our group, and others, had already developed evidence in the areas of cardiovascular disease (CVD) monitoring (cholesterol and blood pressure), warfarin monitoring and the monitoring of diabetic nephropathy.[5,7–10] This programme extended this work to other important clinical areas in primary care that represent two extremes in the way monitoring is carried out in primary care: renal monitoring in chronic kidney disease (CKD) and monitoring people with chronic heart failure (CHF). In the renal monitoring workstream (WS), we emphasised the non-diabetic population with CKD, to complement our previous report on diabetic nephropathy.[7]

Diagnosis and management of CKD is based around estimated glomerular filtration rate (eGFR) measurements (creatinine and cystatin C based). Measurement of eGFR-creatinine (i.e. eGFR based on a creatinine measure) is recommended whenever a request for serum creatinine is made;[11] as laboratory testing in primary care has seen a 9% annual increase in the previous two decades,[12] the majority of those classified with CKD will have mild/moderate disease [G1 to G3b, based on eGFR-creatinine, and A1/A2 based on albumin–creatinine ratio (ACR)]. Therefore, most of the management/monitoring for CKD carried out in primary care will be in this group, with the final stages of disease (renal failure needing dialysis or transplantation) occurring rarely or only after many years. Current National Institute for Health and Care Excellence (NICE) guidance for the management of CKD[11] recommends that monitoring should be based around measurements of eGFR-creatinine and ACR, with the frequency determined jointly by the patient and the health practitioner, but suggests at least one test per year for those with mild or moderate reduction in kidney function (G3a or higher) or for those with moderately increased ACR (A2).

For CHF, on the other hand, diagnosis is carried out by a heart failure multidisciplinary team based around symptoms, signs and investigations. N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) is currently the only recommended test used as part of this diagnostic process, but there

are high levels of uncertainty regarding the threshold used for this.[13] Although some improvement in the management of this condition has been made, the outlook after diagnosis is still poor; therefore, the majority of monitoring, even when carried out in primary care, is conducted in the later stages of disease.[14] There is, however, strong evidence of the prognostic association between NT-proBNP level and survival,[15] as well as evidence that treatment of heart failure can improve patient quality of life, in terms of both physical and emotional well-being.[16] With regard to monitoring, NICE recommends that this should be based around clinical reviews and recommends the use of NT-proBNP as part of treatment optimisation only in a specialist care setting for people with CHF aged < 75 years who have a reduced ejection fraction and who do not have CKD of G3a or higher.[13]

The research programme

The overall aim of this programme is to improve the management of long-term conditions in primary care by optimising the utility and frequency of tests used for monitoring. To achieve this, we carried out a series of inter-related projects on two specific areas, arranged as two WSs: WS1 – CKD and WS2 – CHF. Each WS was designed to (1) provide a summary of current practice and current evidence in this area, (2) generate new quantitative and qualitative evidence for monitoring these conditions and (3) provide a cost-effectiveness framework (or full model) to integrate this evidence.

The programme was integrated by a series of studies using different methodological approaches: systematic reviews, analysis of electronic health records, cohort and feasibility studies, interviews and focus groups, and statistical and health economic modelling. These studies were carried out to answer the following research questions:

- Does the choice of biomarker for the monitoring of CKD in a primary care population better predict renal function decline and is this choice cost-effective?
- Can the number of tests that are used to monitor individuals with stage G2 and G3 CKD be reduced, and hence the associated costs?
- Is it useful to monitor CHF in primary care using natriuretic peptide (NP) or weight as markers?
- Is it feasible and affordable to use point-of-care (POC) NP measurement as part of a monitoring strategy in primary care?
- What is the acceptability and impact of alternative monitoring regimes among individuals experiencing these conditions?

The research was carried out between January 2013 and May 2019.

The links between the different WSs and the different projects in each WS are summarised in *Figure 1*. There was shared methodology in both WSs and a single stakeholder group, which provided guidance and direction throughout.

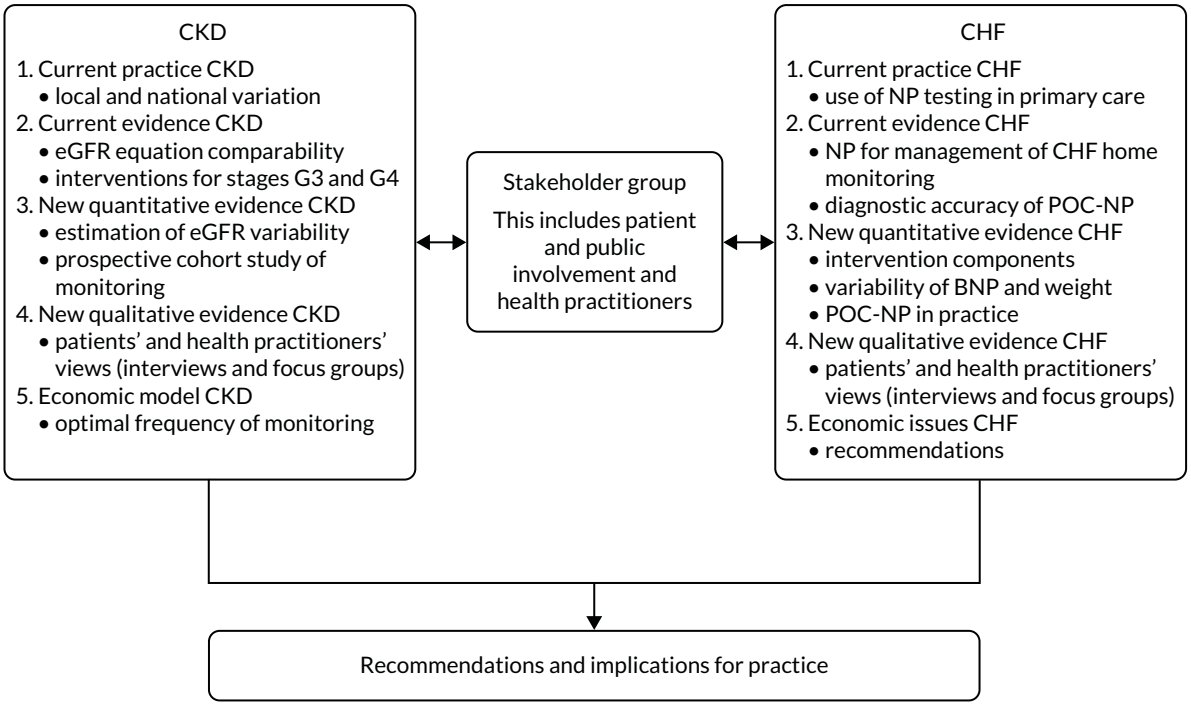

FIGURE 1 Overview of the programme. BNP, B-type natriuretic peptide.

Workstream 1: chronic kidney disease

Prevalence rates from the Quality and Outcomes Framework (QOF) England returns indicate that > 1.8 million adults are classified as having moderate to severe CKD (defined as persistent proteinuria or eGFR from serum creatinine), representing 4.09% of those aged ≥ 18 years.[17] CKD (see *Appendix 1* for the five main stages) is associated with increased CVD risk (predominantly stroke, ischaemic heart disease and heart failure)[2,18–21] and increased all-cause mortality.[2,19,21]

Given that prevalence of CKD rises exponentially with age, published estimates vary according to the populations used to derive them. Less severe stages of early CKD are likely to be more prevalent, as suggested by US data that estimated that approximately 14% of the population could be classified as having stage G1, 10% as having stage G2, 6.7% as having stage G3 and 0.5% as having stages G4 and G5. Nevertheless, the majority of studies focus only on moderate or severe renal impairment, at the level of CKD stage G3+, which means that there is a lack of evidence for the management of the majority of those with CKD.

Most patients with CKD are managed in primary care (98%) using a multifactorial approach of repeated monitoring, maintenance of blood pressure below agreed guideline limits (140/90 mmHg, or < 130/80 mmHg in those with diabetes or raised proteinuria), treatment of hypertension with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and encouragement to lead a healthy lifestyle.[11] Current NICE guidance for the management of CKD[11] recommends that monitoring should be based around measurements of eGFR-creatinine and ACR, with the frequency determined jointly by the patient and the health practitioner and tailored to take into account several factors, but suggests at least one test per year in those with mild or moderate reduction in kidney function (stage G3a or higher) or those with moderately increased ACR (stage A2). One of the reasons given for monitoring people with CKD is to be able to identify accelerated progression, which is currently defined as a sustained decrease in glomerular filtration rate (GFR) of ≥ 25% and change in GFR category within 12 months, or a sustained decrease in GFR of 15 ml/minute/1.73 m^2 in ≥ 1 year. Accelerated CKD progression is one of several potential criteria for hospital referral.[11]

What questions are being addressed?

We studied current practice in monitoring CKD to establish a point of reference for our subsequent research, and we reviewed the evidence for treatment options in CKD, because the value of monitoring depends, in large part, on the availability of actions that can be taken when disease has progressed. The value of monitoring also depends on the strength of the signal (true change) compared with the noise (apparent change due to imprecision in laboratory tests). We therefore studied the signal and noise of the current monitoring test, eGFR-creatinine, using different equations, and used this to compare the value of longer versus shorter intervals between laboratory tests. Furthermore, we established a cohort study in which to compare the laboratory test currently used to calculate eGFR-creatinine with a promising alternative using eGFR-cystatin C (i.e. eGFR based on a cystatin C measure). We accompanied these quantitative studies of the overall properties of CKD monitoring with detailed investigation of the experience of CKD monitoring in practice from patients and health practitioners. This WS addressed the following questions:

- What is current practice in monitoring kidney disease in primary care?
- Is there evidence for preferring the Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation when estimating eGFR-creatinine?
- What interventions are known to slow the progression of early-stage CKD?
- What are the properties of CKD monitoring based on eGFR-creatinine, in particular the rate of change and the accuracy of diagnosed CKD stages?

- Does the use of serum cystatin C (instead of serum creatinine) to estimate GFR improve the predictive value of CKD monitoring?
- What are the views from patients and health practitioners on how monitoring CKD is carried out in primary care and the acceptability of any changes from current practice?
- What is the cost-effectiveness of different monitoring strategies for CKD in primary care?

Current practice

Serum creatinine testing 1993–2013 in Oxfordshire (Oke et al.[22]*)*

To determine if the frequency of kidney function testing has changed over time, we looked at who is tested and how frequently these tests are conducted (see *Appendix 2*). We obtained details of serum creatinine tests sent to the Oxford University Hospitals NHS Foundation Trust Clinical Biochemistry laboratories from both primary and secondary care in Oxfordshire (> 1.2 million people) over a 20-year period (1993–2013). To determine the frequency of monitoring, we used Poisson regression models to adjust for the initial level of kidney function, glycated haemoglobin (HbA_{1c}) testing, evidence of albuminuria or proteinuria, sex and age.

We found that the number of serum creatinine tests ordered from primary and secondary care steadily increased over the 20-year period (reaching > 220,000 in 2013 in primary care alone). Increased rates of testing were attributed, in part, to the expansion of the area that the laboratory serves and the ageing population, but trends did not seem to be affected by guideline changes or incentive payments. Older people with higher HbA_{1c} levels and people with reduced kidney function were tested most frequently.

This analysis did not include data on patient history, prescriptions or reasons for test ordering, and so was unable to determine whether the tests were for diagnosis or monitoring or whether or not they were ordered with appropriate frequency. As the data are from a single region of the UK, we were unable to comment on whether or not these represent nationwide trends.

Therefore, we looked at national data to examine kidney function testing using data from > 600 general practices across the UK.

UK primary care kidney function testing 2005–2013 (Feakins et al.[23]*)*

To comment on regional variation in kidney function testing rates and how these differ by chronic diseases and prescriptions, we used routinely collected data from 4,573,275 patients from 630 UK general practices contributing to the Clinical Practice Research Datalink (CPRD) between 2005 and 2013 (see *Appendices 3* and *4*). The analyses were based on serum creatinine and urinary protein measures as markers of kidney function, and codes indicating the presence of chronic conditions, as well as drug prescriptions for which kidney monitoring is recommended.

We found that the rate of serum creatinine testing increased linearly across all age groups year on year, and the rate of proteinuria testing increased sharply in the 2009–10 financial year, but only for patients aged ≥ 60 years. For patients with established CKD, creatinine testing increased rapidly in 2006–7 and 2007–8, and urinary protein measurement increased rapidly in 2009–10, aligning with the introduction of respective QOF indicators. In adjusted analyses, the presence of a Read code for CKD was associated with up to a twofold increase in the rate of serum creatinine testing, whereas the presence of other chronic conditions and the prescription of potentially nephrotoxic drugs were associated with up to a sixfold increase. Regional variation in the rate of serum creatinine testing predominantly reflected country boundaries; in particular, Northern Ireland had higher rates of testing than other UK regions.

These findings suggest that the significant increases in the number of patients having kidney function tests annually and the frequency of testing are driven by changes in the recommended management of CKD in primary care, namely the QOF. Future studies should address whether or not increased testing has led to better outcomes.

Current evidence

Comparison of the bias and accuracy of the Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration Equations (McFadden et al.*[24])*

Measuring eGFR is important in primary care as it determines the stage of CKD, referral decisions and changes to doses of commonly prescribed medicines. However, there is uncertainty over the optimal eGFR-creatinine equation to be used in community-based populations because the existing equations for eGFR-creatinine are derived mainly from younger patients with renal disease, whereas, in community populations, the patients are older and have a lower prevalence of established renal disease. We set out to examine how eGFR from existing equations, the CKD-EPI and MDRD, differ from measured glomerular filtration rate (mGFR) in populations that are equivalent to a primary care population (see *Appendix 5*). We undertook a systematic review and meta-analysis of studies (up to June 2017) that recruited patients similar to a primary care population, extracting data on the difference between estimated and measured GFR for CKD-EPI and MDRD equations. We also developed methods for meta-analysis to combine data on differences into summary statistics.

We found that the MDRD equation underestimates true renal function by 4.7 ml/minute/m^2 [95% confidence interval (CI) 0.8 to 8.7 ml/minute/m^2], and the CKD-EPI equation is more accurate in community-based populations. At higher levels of mGFR, which reflect community populations, the MDRD equation was less accurate (by 4.6%, 95% CI 2.9% to 6.2%) and more biased (by 3.2 ml/minute/1.73 m^2, 95% CI 1.6 to 4.8 ml/minute/1.73 m^2) than the CKD-EPI equation. Our data were limited in that the quality rating was not deemed high in many studies that were single centre, and the recruitment methods were not always clearly stated. This work allowed us to have a baseline of bias and accuracy for creatinine-based estimates of GFR in primary care.

Effects of medication on the progression of stages G3 and G4 chronic kidney disease (Taylor et al.*[25])*

Treatment of people with CKD aims to prevent or reduce disease progression, prevent complications and minimise the risk of CVD (see *Appendix 6*). We conducted a systematic review and meta-analysis of randomised controlled trials (RCTs) (March 1999 to July 2018) to examine and compare the effects on the progression of CKD of four classes of drugs: antihypertensives, lipid-modifying drugs, glycaemic-control medications in patients with diabetes, and sodium bicarbonate. Our focus was on patients managed in primary care or by shared care with specialist nephrology services. The review summarised 35 studies including > 51,000 patients: 12 studies of antihypertensive drugs, 14 of lipid-modifying drugs, one study of an antihypertensive drug and a lipid-modifying drug, six studies of glycaemic-control drugs, and two of sodium bicarbonate. Nineteen studies provided summary data based on populations with CKD of stages G3 and G4 only. None of these studies provided data on sodium bicarbonate medication. Pooled estimates from these showed that, for antihypertensive drugs, there were no significant differences in renal function, and that eGFR was 4% higher in those taking lipid-modifying drugs (ratio of means 1.04, 95% CI 1.00 to 1.08) and 6% higher (ratio of means 1.06, 95% CI 1.02 to 1.10) in those taking glycaemic-control drugs (no studies provided data on sodium bicarbonate medication). Furthermore, and as expected, treatment with lipid-modifying drugs led to a significant reduction in the risk of CVD [risk ratio (RR) 0.64, 95% CI 0.52 to 0.80] and all-cause mortality (RR 0.74, 95% CI 0.56 to 0.98). There were no significant differences in cardiovascular events or mortality in studies of antihypertensive and glycaemic-control drugs. We found some evidence that glycaemic-control and lipid-modifying drugs slow the progression of CKD, and no evidence of renal benefit or harm from antihypertensive drugs.

New quantitative evidence

Modelling deterioration of kidney function (Oke et al.[26])

This project (see *Appendix 7*) aimed to estimate the rates of progression of renal function stratified by urine albumin status, age and sex in a general population of people attending primary care.

We used the CPRD and constructed four cohorts based on their urine albumin status at baseline. The statistical method specified in the protocol (based on linear models[6,27]) proved unsuccessful; instead, a method for categorical data (i.e. a hidden Markov model[27]) was used to estimate the true underlying kidney function while accounting for measurement error and within-person variability due to eGFR-creatinine. Models were adjusted for age, sex, heart failure and previous diagnosis of cancer, and stratified by albuminuria status (< 3 mg/mmol vs. 3–30 mg/mmol vs. > 30 mg/mmol) at baseline.

The estimated rate of true transition from one CKD stage to the next, per year, was approximately 2% for people with normal urine albumin, between 3% and 5% for people with microalbuminuria (urine albumin of 3–30 mg/mmol) and between 3% and 12% for people with macroalbuminuria (> 30 mg/mmol). Misclassification of CKD stage due to measurement variability in serum creatinine, and hence eGFR-creatinine, is estimated to occur in between 12% and 15% of all tests in primary care. Progression of kidney function becomes faster with increasing age, and is faster among men, among people with elevated urine albumin and among patients with heart failure or with a previous diagnosis of cancer.

The true rate of progression of CKD is relatively slow, and eGFR-creatinine is an imperfect measurement that can lead to misclassification of disease stage every time it is used. This suggests that, when annual monitoring detects an apparent change of disease stage, this is more likely to be attributable to the imperfections of the measurement than to a true change.

Limitations of this analysis include missing data, which arise from the use of routinely collected electronic health records data rather than a clinical study. See the following section for a further study of the progression of CKD.

Prospective cohort study of monitoring chronic kidney disease

Cross-sectional evidence suggests that cystatin C provides better estimates of current kidney function than serum creatinine. We designed a study [Frequency Of Renal Monitoring – Creatinine and Cystatin C (FORM-2C)] to investigate whether or not cystatin C also provides better prognostic information than serum creatinine for future change in renal function. Because direct (radiological) measurement of GFR is invasive and expensive, making large studies impractical, we used change in eGFR (respectively eGFR-creatinine and eGFR-cystatin C) as the study outcome: the study report in *Appendix 8* gives more details.

A cohort of 747 patients with an eGFR-creatinine of 30–89 ml/minute/1.73 m^2 was recruited and followed up for 2 years, with blood samples taken at recruitment, 2 weeks and 12 weeks to establish baseline eGFR (both measures), and at 6, 12, 18 and 24 months after recruitment to measure the change in eGFR (both measures) over time. There were sufficient data from 629 patients to carry out analysis. When using serum creatinine to estimate GFR, baseline eGFR-creatinine had a concordance statistic (*c*-statistic) (also known as concordance index) of 0.495 (95% CI 0.471 to 0.521) for predicting future change in eGFR-creatinine. When using cystatin C to estimate GFR, baseline eGFR-cystatin C had a *c*-statistic of 0.500 (95% CI 0.474 to 0.525) for predicting future change in eGFR-cystatin C. Similar results were seen in sensitivity analyses, as described in *Appendix 8*. Either method of estimating baseline eGFR was predictive of the 2-year value [*c*-statistic for eGFR-creatinine 0.833 (95% CI 0.811 to 0.851) and for eGFR-cystatin C 0.889 (95% CI 0.877 to 0.898)], because there was, on average, little change over 2 years (see *Appendix 8*, *Table 9*).

Regardless of the method of estimation, eGFR (both measures) does not appear to usefully predict future change in eGFR (both measures). This is relevant, as change in eGFR has been shown to be significantly associated with all-cause mortality, end-stage renal disease (ESRD), and cardiovascular events beyond that observed for mGFR.[28,29] The study is limited by the use of surrogate measurements of renal function in the outcome, as well as in the index tests. One study using radiological measurement of kidney function is due to report in June 2021. If confirmed, our preliminary results suggest that the rate of change of renal status does not depend strongly on current state: there is no 'acceleration' of renal decline, at least across CKD stages G2 and G3a, which dominate our cohort.

New qualitative evidence

Qualitative evaluation for chronic kidney disease

To understand the acceptability and impact of current monitoring regimes among individuals with CKD, we used a mixture of patient interviews and focus groups with health professionals[30] (see *Appendices 9* and *10*). For the patient interviews, we sought to recruit people who were having regular checks of their kidney function because they had stage G1–3 CKD. For the focus groups with health professionals, we used a variety of methods to recruit participants, mainly drawn from practices in Oxfordshire and the wider Thames Valley area. Participant numbers for the focus groups were small, so the views expressed may not necessarily be regarded as representative of these professions.

Forty-six people were recruited for the patient interviews; one withdrew after interview. Stage of CKD was unknown for seven participants, 35 had stage G3, two had stage G2 and two had been recently referred to specialist care because of more advanced kidney disease. The main findings were published in 2015 on https://healthtalk.org/ (accessed 5 May 2020) as 'topic summaries'.[31] Sixteen people participated in four health professionals' focus groups.

A gap was revealed between what health professionals seek to explain about CKD and what patients may understand. Primary care professionals often avoided using the term 'CKD' when talking to patients with early-stage kidney impairment in an attempt to avoid causing unnecessary anxiety. Patients' accounts of receiving information about their kidney health echoed the phrases described by health professionals. However, patient interpretations showed some of these phrases to be unhelpful, raising further questions and adding to, rather than diminishing, initial concerns. The use of phrases such as 'kidney damage' or 'kidney failure' could be frightening, and the term 'chronic' was sometimes misinterpreted as meaning serious, whereas a description of the decrease in kidney function as a percentage or stage seemed less alarming. However, the exact meaning of the test results was often unclear, and those who were told their CKD stage did not always understand what this meant. Some patients found it difficult to understand that they had been diagnosed with CKD when they did not experience symptoms. Attempting to reassure patients that their kidney impairment was nothing to worry about, without providing explanatory information about the condition, could leave patients concerned and wanting to know more about possible causes, the meaning of test results and whether or not they could do anything to prevent further decline.

The GPs all confessed to being unfamiliar with the latest updates to NICE guidelines for either CHF or CKD or both, arguing that work pressures did not allow time to read these for all conditions. NICE's website was considered confusing and difficult to navigate, and GPs were more likely to learn about patient management recommendations from other sources, such as the Clinical Commissioning Group or QOF alerts. On the current CKD guidelines,[11] specifically, there was confusion about when ACRs should be requested from the laboratory and how the results should be interpreted and acted on.

Our research led to a mixed-methods study that calls for a rethink in how doctors talk to patients with reduced kidney health, replacing the term 'CKD' with different bands of kidney age (see *Appendix 11*).

Economic models

Review of economic models

We asked the following questions: what is known, from existing models, about the cost-effectiveness of monitoring of CKD? What can be inferred about the cost-effectiveness of CKD monitoring from the results of our CKD WS project (described above)? To what extent has the cost-effectiveness of CKD monitoring been studied, and, in particular, what modes of CKD monitoring have been studied? What modes of CKD monitoring should be prioritised for study (see *Appendix 12*)?

We reviewed the literature to identify existing cost-effectiveness models in CKD that could be suitable for such an assessment (up to January 2019). Although there are many model-based evaluations of interventions in CKD, we included only models that could be useful to evaluate the cost-effectiveness of CKD monitoring in the context of current clinical guidelines. Therefore, a lifetime cost-effectiveness model was reviewed if (1) CKD stages were defined using eGFR-creatinine (i.e. not exclusively based on proteinuria status), (2) at least two distinct states prior to renal replacement therapy (RRT) (i.e. renal dialysis or renal transplant) were included (i.e. the model states were not simply 'pre RRT' and 'RRT') and (3) the incidence of important cardiovascular events was modelled.

A pearl-growing search strategy was used to identify eligible cost-effective models. First, four suitable key studies ('pearls') were identified[32–36] by the authors using their previous experience, including the development of one of these models.[36] The reference lists and citations of each included study were reviewed. One additional study was included[37] and classified as a new pearl, and the search was repeated for another iteration, as a result of which no relevant papers were identified. To ensure that no important manuscripts were missed, a quick scoping search was performed in Google Scholar (Google Inc., Mountain View, CA, USA) (using the search line 'cost-effectiveness "chronic kidney disease" progression'), followed by a review of the references included in an in-house review of models of CKD progression (Iryna Schlackow, University of Oxford, 2018, personal communication). These reviews did not yield further eligible studies.

Thus, five long-term cost-effectiveness models potentially useful to assess CKD monitoring were reviewed. Detailed descriptions of the models included in our review are presented in *Appendix 12*. Of the five models, two were developed to assess the cost-effectiveness of CVD prevention interventions (e.g. statins) in CKD,[32,36] two were developed in the context of screening for CKD/proteinuria in general population[33,37] and one aimed to accommodate both CKD identification and treatment.[35] Parameters of the models were mostly collated from published literature and/or derived from different data sources,[32,33,35,37] with only one model based largely on individual patient-level data.[36] Only two models separate the ESRD state into dialysis and renal transplant states, which are associated with different outcomes and costs.[35,36] All models included validation of their performance, but this validation was not in the context of a general CKD population. Only the screening models included early CKD stages (e.g. CKD stage G2, which constitutes the bulk of the CKD population in a primary care setting) in their target populations.[33,35,37] The CVD prevention models considered only CKD stage G3 and beyond.[32,36] In the screening models, effects of ACE inhibitors and ARB treatments were implemented, but in only one model were these treatments assumed to affect CVD risks;[37] in the other two models, these treatments were assumed to affect only CKD progression and mortality.[33,35] Only one model considered heart failure as an end point,[35] but it was unclear how the treatment effect on heart failure was implemented, and what the impact of this treatment on other transitional probabilities was. None of the identified studies assessed effects of monitoring eGFR.

In summary, none of the identified models included the elements required for the assessment of cost-effectiveness of monitoring strategies in UK primary care. Therefore, it was decided to develop a new cost-effectiveness model to support the evaluation of CKD monitoring.

Cost-effectiveness of monitoring kidney function in UK primary care (Schlackow et al.[38] *and* Appendix 14*)*

We sought to incorporate the findings from the programme into a model of the cost-effectiveness of monitoring CKD in primary care. We assessed the following frequencies of GFR monitoring: no monitoring, monitoring every 5, 4, 3 and 2 years and annual monitoring. Based on the systematic review of interventions (see *Appendix 6*),[25] other published meta-analyses[39–41] and discussions with clinicians and stakeholders, it was agreed that a key objective of eGFR monitoring in primary care is to guide treatments to reduce CVD risk among people with reduced kidney function. To project health outcomes, we supplemented the model of variability and progression (see *Appendix 7*)[26] with additional modelling that included CVD risk equations with a term for stage of eGFR. Full details of the model, including estimated cost and quality-of-life impact of cardiovascular outcomes, are given in Schlackow *et al.*[38]

Appendix 14 gives details of the application of the model to GFR monitoring, including the assumptions made about monitoring costs and prescription costs, and assumptions made about treatment. Current clinical guidelines recommend that CVD preventative treatments (i.e. statin, antihypertensive or antiplatelet drugs) be considered for patients with reduced kidney function and, therefore, in the cost-effectiveness analysis we studied the impact of GFR monitoring on their use. Based on the systematic review of interventions (see *Appendix 6*),[25] we assumed statin treatment to be the most relevant.

We could not justify monitoring in people with CKD to guide cardiovascular prevention as changes in eGFR did not trigger changes in CVD treatment recommendations (see *Appendix 14*). Briefly, this arises because, for people with clinical CKD [i.e. meeting the Kidney Disease: Improving Global Outcomes (KDIGO)[42] definition], statin treatment is recommended;[43] many of them are also indicated for antihypertensive treatment[44] and, if they have a history of CVD, for antiplatelet therapy.[44] These therapies are also widely recommended in people with CVD.[43] Therefore, under current guidelines,[11] monitoring the eGFR among patients with clinical CKD or with a history of CVD would largely not change indicated cardiovascular therapies.

We also considered eGFR monitoring in people with impaired eGFR (i.e. an eGFR of < 90 ml/minute/1.73 m^2) but no CKD (defined as macro/microalbuminuria or an eGFR of < 60 ml/minute/1.73 m^2). For some of these people, monitoring eGFR to detect CKD is potentially beneficial, compared with no monitoring, but the model does not currently separate potential harms of overdiagnosis. The optimal (i.e. most cost-effective) interval of eGFR monitoring in this group depends on a patient's age and our analyses indicate that, at £20,000 per QALY cost-effectiveness threshold, that is about every 3 years for people aged < 60 years, every 4 years for people aged 60 to 69 years, and no monitoring among those aged ≥ 70 years.

Conclusions

This WS focused on management/monitoring of CKD in primary care, researching current practice and providing new evidence to guide this management. In particular, we concluded that:

- Over the last decade, renal function testing has increased in volume at the national level. Specifically, for those with CKD, this increase is driven by national guidance for reporting monitoring.
- At higher levels of mGFR, which reflects primary care populations, the MDRD equation was less accurate and more biased than the CKD-EPI equation.
- Lipid-modifying and glycaemic-control medications are possibly beneficial to slow the progression of early-stage CKD. However, evidence of glycaemic control exists only in diabetic populations.
- The rate of change in eGFR is slow, and misclassification is more common than real change.

- The rate of change in eGFR is slow, regardless of the baseline eGFR, in patients in primary care. Cystatin C is not a better predictor of change than creatinine.
- The terminology around 'chronic' and 'disease' is problematic for patients and GPs when communicating about early stage, or small decreases in renal function.
- Before this programme, there were no models available that were able to assess the cost-effectiveness of monitoring strategies in UK primary care, to our knowledge.
- A new cost-effectiveness model to assess frequency of eGFR modelling was developed in this programme; people with an eGFR of between 60 and 90 ml/minute/1.73 m^2 were identified as a group for whom monitoring could potentially be beneficial.
- Application of our cost-effectiveness model to those with an eGFR of between 60 and 90 ml/minute/1.73 m^2 suggests that monitoring eGFR in people aged < 70 years and without cardiovascular disease every 3–4 years to guide cardiovascular prevention may be cost-effective.

Research recommendations

- Estimates of the bias, and accuracy, of eGFR-creatinine equations varied greatly (statistical heterogeneity) between studies in our systematic review. It would benefit the NHS to determine when (in what settings) and how (with what protocol) the most accurate results can be obtained and which protocol should be recommended nationwide.
- High variability in eGFR-creatinine, and hence inaccuracy in CKD staging, suggest a probable benefit to combining eGFR measurements (several creatinine and/or several cystatin C), rather than simply repeating them and acting on the most recent; this potential route to better management should be researched.
- Cystatin C appears to have some advantages over serum creatinine for estimating GFR, for example in predicting rapid progression; these findings, from secondary analyses only, should be confirmed.
- At least one alternative to the term 'CKD' has now been proposed, in response to our qualitative work and patient and public involvement (PPI), and its potential to improve communication should be investigated (see *Patient and public involvement*).
- Closing the gap (identified in the systematic review of interventions) of evidenced interventions that specifically protect renal function would have the greatest potential to improve the cost-effectiveness of CKD monitoring.

Overall, these can be summarised as three key questions:

1. When and how can the most accurate estimates of GFR be obtained?
2. What is the longer-term relationship between current eGFR (either measure) and future progression of CKD?
3. How can the progression of CKD be prevented or delayed in patients at risk?

Implications for practice

- Laboratories could improve the accuracy of eGFR testing by switching to the CKD-EPI equation for its calculation, as recommended by NICE,[11] if they have not done so already.
- Potential treatments that might positively affect kidney function are lipid-modifying treatment and glycaemic-control medication.
- The rate of change of kidney function in a primary care population is slow, and most apparent changes will be due to measurement noise (error) and not real change.
- This rate of change is slow regardless of the initial CKD stage (in a primary care population).
- The terms 'chronic' and 'disease' act as barriers in the communication between health practitioners and patients. A potential solution is the use of alternative terms, such as 'kidney age'.[45]
- Monitoring individuals with CKD is difficult to justify by the usual logic of treatment initiation or titration. Alternative ways of quantifying its benefit might be required.

Reflections

We find that CKD monitoring, using blood tests in particular, but also urine tests, has been a huge growth area in the NHS. However, our research highlighted a substantial gap in the evidence base for this monitoring. The usual rationale for monitoring a clinical condition includes an action, typically a treatment change, that can be taken in response to the results of monitoring tests. In a large systematic review, we found no evidence that antihypertensive treatment or administration of sodium bicarbonate are useful actions to slow progression of kidney disease, and the treatments that might slow progression, in particular lipid-modifying treatments, are likely to be in use already in patients with CKD, particularly those with stage G3 disease onwards. Following these findings through to a full model of cost-effectiveness emphasised that monitoring of CKD in primary care, especially as frequently (i.e. annually) as currently recommended, cannot be rationalised as monitoring to guide treatment. This complements our previous finding that monitoring diabetic nephropathy as frequently as annually is unlikely to be cost-effective.[7]

It would, however, be premature to abandon all monitoring of CKD. Arguments may be made that monitoring CKD (e.g. in stage G3) could encourage lifestyle changes, promote adherence to already indicated medications, help avoid nephrotoxic treatments such as ibuprofen in primary care and help avoid sudden descent from apparent full kidney health into late-stage kidney disease in secondary care. These benefits will be harder to quantify than an obvious treatment for CKD, but such a research effort is needed to provide a sound rationale for monitoring and to design a cost-effective monitoring schedule. Current practice, that is annual monitoring, has become a growing cost to the NHS, yet lacks a clear evidence base.

The other major finding to emerge from this work was the problematic terminology ‘CKD’, which is misunderstood by patients and avoided or used with reluctance by GPs. This emerged from our formal qualitative research, but it emerged also, and sooner, from the reactions of patients approached to take part in our studies, and from the patient and public members of our stakeholder group. We return to this in *Patient and public involvement*.

Workstream 2: chronic heart failure

A 2002 report suggested that ≈ 900,000 people in the UK had CHF.[46] Since then, the prevalence of heart failure in the UK has been increasing, probably as a result of demographic changes and improvement in the management of CHF, with an observed increase of 23% between 2002 and 2014.[47] In a prospective community screening study,[48] definitive CHF, according to the European Society of Cardiology (ESC) criteria,[49] was present in 2.3% of the population, of whom the proportion with a left ventricular ejection fraction (LVEF) of < 40% was 41%; the prevalence of definitive CHF rose to 8% in those aged > 75 years.[50]

The incidence in the UK is less clear, but the crude rate has been estimated to be 1.3 cases per 1000 population per year for those aged ≥ 25 years, reaching 7.4 cases per 1000 population per year for those aged 75–84 years and 11.6 cases per 1000 per year for those aged ≥ 85 years.[48] The absolute incidence of CHF in the UK has also increased considerably since 2002 (12% between 2002 and 2014), even though the age-standardised incidence is actually decreasing.[47] Overall, a GP with a patient population of 2000 will care for approximately 40 to 50 patients with heart failure and see two or three new cases each year.

Early diagnosis is seen as critical because early-stage heart failure may be reversible. However, the diagnosis and management of CHF remains challenging. For example, although CHF is frequently diagnosed by GPs, it is confirmed by echocardiography in only approximately one-third of cases.[51] NICE[13] recommends that a heart failure multidisciplinary team carry out the CHF diagnosis using a combination of symptoms, signs and investigations. The use of a NT-proBNP measure is the only biomarker recommended as part of this diagnostic process, but with recognition of the uncertainty regarding the absolute threshold used.[13] Despite recent improvements, patients diagnosed with heart failure have a poor prognosis: approximately 40% of patients diagnosed die within the first year. After that, the mortality rate decreases to approximately 10% per year.[52–54] Survival rates are worse than those of cancer of the breast or prostate.[55]

People diagnosed with heart failure have high levels of use of health-care resources not only in terms of GP consultations and community-based drug therapies, but also because of referrals to outpatient clinics and inpatient bed-days. Heart failure accounts for 5% of all emergency medical admissions; it is estimated that the total annual cost of heart failure to the NHS is approximately 2% of the total budget, with approximately 70% of this total attributable to the costs of hospitalisation.[56,57] Moreover, re-admissions are common, with approximately one in four patients re-admitted within 3 months.[58,59] Patients also report a dramatic decrease in their quality of life, with a consequent impact not only on agencies such as social services and the benefits system, but also on their families and caregivers.[58] There is, however, considerable evidence[58,60,61] that pharmacological treatments can improve the prognosis of heart failure. Both pharmacological and non-pharmacological treatments can improve patient quality of life, in terms of both physical functioning and well-being.[58]

With regard to monitoring, NICE[13] recommends that this should be based around clinical reviews, and recommends the use of NT-proBNP as part of treatment optimisation only in a specialist care setting for people with CHF aged < 75 years who have reduced ejection fraction and who do not have CKD of stage G3a or higher.[13] Increased levels of B-type natriuretic peptide (BNP) and NT-proBNP in patients with heart failure have been demonstrated, in some studies,[62,63] to have, not only diagnostic, but also prognostic, utility.

Previous work has identified BNP as having large clinical variation in non-severe populations, thereby probably reducing its utility for monitoring CHF.[64] POC NP testing has been suggested as an alternative method to reduce this variability.[65] At the same time, POC NP testing would enable GPs to rapidly refer the appropriate patients or, if CHF can be excluded, investigate alternative causes of clinical symptoms (e.g. dyspnoea).

What questions are being addressed?

We reviewed the evidence for NP-guided treatment in CHF, including how a potential intervention using this approach could be implemented, because this has been the most promising area for which monitoring of this group could be effective. For NP monitoring to be of use, the noise (i.e. within-person variability) should be relatively small compared with the signal (true change). We therefore studied the noise of NP measures based on a secondary analysis of a clinical trial. As an alternative strategy, to minimise NP variability, we studied the accuracy of available POC NP devices, as well as testing the feasibility of their use in a general practice. To understand where monitoring should take place, we summarised the evidence relating to strategies for remote monitoring (RM) (from home) in this population. As for the CKD WS, we carried out a detailed investigation of the experience of CHF monitoring in practice from the perspectives of patients and health practitioners. Finally, we summarised the evidence available regarding health economic models to evaluate monitoring strategies in CHF and provided a framework to carry out this assessment. This WS addressed the following questions:

- Is there evidence to suggest that NP-guided treatment improves outcomes in patients with CHF?
- What would be the relevant components of an intervention to implement NP-guided treatment?
- What are the properties of NP measures used when monitoring CHF, in particular, the within-person coefficient of variation (CV)?
- Are POC NP measures accurate and, of the devices available for measuring POC NP, which would be best to use?
- Is it feasible to implement a POC NP test/device in a primary care practice?
- What is the evidence regarding the efficacy of RM in CHF?
- What are the views from patients and health practitioners of how monitoring CHF is carried out in primary care and the acceptability of any changes to current practice?
- What health economic models have been used, and what issues need to be addressed, to study the cost-effectiveness of monitoring CHF in UK primary care?

Current practice

Although the age-adjusted heart failure incidence in the UK is decreasing, the absolute incidence and prevalence have seen a substantial increase over the previous decade, potentially due to demographic changes and improvement in management.[47] Recommended management of CHF patients is based around a multidisciplinary team working in collaboration with primary care, with the primary care team taking over routine management once the patient has stabilised.[13] Measurement of patient NT-proBNP is also recommended as part of the diagnostic pathway and as part of a monitoring strategy to optimise treatment, but only in a specialist setting for people aged < 75 years with heart failure, with reduced ejection fraction and with an eGFR of > 60 ml/minute/1.73 m^2.

An analysis of current management of CHF patients in primary care[66] identified that, at least until 2013, only a small proportion of those with a current diagnosis of CHF have ever had NP measured in a primary care setting (4.85%, 95% CI 4.71% to 4.99%); that most of these measurements are probably used as part of a diagnostic strategy (74% of individuals with a single NP measurement); and that the type of NP most commonly used in primary care since 2007 is NT-proBNP. This analysis[66] confirmed the strong association observed between high levels of NPs and all-cause mortality in this group. It also suggests that measurements of NP are underused in primary care as part of the diagnostic pathway (not consistent with NICE guidance[13]) and not used as part of a monitoring strategy (consistent with NICE guidance[13]).[66]

Current evidence

Natriuretic peptide-guided management of heart failure (McLellan et al.*[67,68])*

We carried out a systematic review and meta-analysis (see *Appendices 15* and *16*) to assess whether or not treatment guided by serial NP monitoring improves outcomes, compared with treatment guided by clinical assessment alone (up to November 2017). In 2016, we found inconclusive evidence for a reduction in all-cause mortality (13%) and heart failure mortality (16%). Heart failure admission was reduced 30% by NP-guided treatment, but the evidence was inconclusive for all-cause admission. Six studies reported on adverse events; however, the results could not be pooled. Only four studies provided results for cost of treatment: three of these studies reported a lower cost for NP-guided treatment, whereas one reported a higher cost. The evidence showed uncertainty for quality-of-life data. Heterogeneity was low for all outcomes bar heart failure admission, which was substantial.

In 2017, the addition of the Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) study[69] increased the total number of participants by 24% and substantially increased the precision of the estimates. This altered the findings of the Cochrane systematic review,[67] and the evidence now indicated that NP-guided treatment could improve all-cause mortality by 13%. The effect on heart failure admission was a relative reduction of 20%, whereas the findings for all other outcomes were similar to those from the Cochrane systematic review.

We concluded that the current pooled evidence indicates a beneficial effect of NP-guided therapy on all-cause mortality and heart failure admissions. However, despite the publication of the GUIDE-IT study,[69] the largest in this field, the effectiveness estimated from the meta-analysis is marginal and the conclusions are not yet robust, with a high chance that these will change as new evidence emerges.

Effectiveness of remote monitoring for heart failure

Remote monitoring, a collective term for telemonitoring (TM) and structured telephone support (STS), of heart failure is increasingly becoming an option for patients, as a result of the ongoing advancement in technology and familiarity with its use (see *Appendix 17*). RM aims to collect and transmit physiological data through devices in the patient's own home that could potentially increase early detection of clinical deterioration, improve patients' quality of life and decrease health-care delivery costs.

Despite the lack of NICE-recommended use of RM (2010[70] and 2018[13] guidelines), the NHS Technology Enabled Care Services Resource for Commissioners,[71] in response to the NHS *Five Year Forward View*,[72] recognised that RM technology would be important in the future.

This systematic review and meta-analysis (up to February 2019) aimed to evaluate the clinical effectiveness of home TM and/or STS interventions, compared with standard care, among adults with heart failure for all-cause mortality, all-cause hospital admission, heart failure hospital admission, length of stay, health-related quality of life, adherence, acceptability, heart failure knowledge and self-care. This was an update of a previous review by Inglis *et al.*[73]

We identified 12 new RCTs, including the second- and fourth-largest studies to date, to our knowledge, to add to the existing 41 RCTs previously identified by Inglis *et al.*[73] in 2015. Screening and data extraction were carried out by two co-authors. For binary outcomes, we used fixed-effects meta-analyses to estimate the RR; for continuous outcomes, the standardised mean difference (SMD) was used.

The pooled results suggest that the rates of all-cause mortality and heart failure hospital admissions were reduced and quality of life was improved with the use of RM (all-cause mortality: STS – RR 0.85, 95% CI 0.76 to 0.96; $I^2 = 0\%$; TM – RR 0.82, 95% CI 0.73 to 0.92; $I^2 = 20\%$; heart failure admission: STS – RR 0.85, 95% CI 0.77 to 0.93; $I^2 = 27\%$; TM – RR 0.74, 95% CI 0.64 to 0.84; $I^2 = 17\%$; quality of life: STS – SMD 0.13, 95% CI 0.09 to 0.18; $I^2 = 86\%$; TM – SMD 0.24, 95% CI 0.20 to 0.28; $I^2 = 98\%$).

However, although there was a suggestion that the rate of all-cause hospital admissions may be reduced by RM, this was not statistically significant. It was not possible to pool data for length of stay, adherence, acceptability, heart failure knowledge or self-care. For the outcomes of all-cause mortality and heart failure hospital admission, the heterogeneity was low and, although moderate for all-cause hospital admission, no particular explanation for the higher heterogeneity was revealed by subgroup analysis or meta-regression. The findings for quality of life should be viewed with caution as the heterogeneity was very high and testing of the robustness of the effect estimate by using a random-effects model resulted in the TM finding no longer being statistically significant.

This is a rapidly changing area of research, and a further 24 studies were recorded as ongoing; therefore, the evidence will continue to need updating as these are published. Furthermore, the technology continues to advance, meaning further updates will be required. Many RM interventions are complex, and further investigation of these using component analysis would be beneficial.

Diagnostic accuracy of point-of-care natriuretic peptide tests for chronic heart failure (Taylor et al.*[74])*

To assess the diagnostic accuracy of POC tests compared with echocardiography, clinical examination or combinations of these, we conducted a systematic review and meta-analysis (up to March 2017) of all POC NP diagnostic accuracy studies (see *Appendix 18*). We included only studies that were carried out in primary care or other ambulatory care settings, as this is where the test would be used in practice.

We identified 42 publications of 39 individual studies and included 37 studies in the analysis. These studies assessed the diagnostic accuracy of two different natriuretic tests (BNP and NT-proBNP); only five studies had been undertaken in primary care. The studies varied considerably in the types of patients they included, the health-care settings and the thresholds used. There was a wide range of sensitivity and specificity at different thresholds reported in the various studies. For the BNP test, the pooled sensitivity and specificity were 0.95 (95% CI 0.91 to 0.97) and 0.57 (95% CI 0.43 to 0.70), respectively, whereas, for NT-proBNP, pooled sensitivity and specificity were 0.99 (95% CI 0.57 to 1.00) and 0.60 (95% CI 0.44 to 0.74), respectively. However, it was important to note that the sensitivity was more variable in the studies conducted in primary care.

Our review showed that NP tests have variable ability to exclude CHF in patients in ambulatory care. A positive test would need to be confirmed with cardiac imaging and also appropriate follow-up. We also highlighted that certain thresholds recommended by guidelines might be relevant, but further research is needed to confirm which thresholds are the most appropriate in an ambulatory care setting and whether or not implementing them can improve patient care.

Limitations of the analysis were that very few data were available in primary care settings and only a small number of studies were conducted using NT-proBNP. Several included studies were also at unclear risk of bias, which may potentially lead to an overestimate of the accuracy measures. The heterogeneity across the studies may also affect the generalisability of the results.

Given the lack of studies in primary care and the methodological limitations we identified in the studies, high-quality evidence in the form of randomised trials is needed to better guide the use of POC NP tests in the primary care and ambulatory care setting. Such studies should also clarify the appropriate thresholds to improve outcomes in patients with CHF. As part of this programme grant, a study in primary care of the accuracy of POC NT-proBNP tests was undertaken to address this research gap.

New quantitative evidence

Essential components in natriuretic peptide-guided management of heart failure (Oke et al.[75])

This work aimed to identify the key components of NP-guided treatment interventions that reduced rates of hospitalisation in patients with heart failure (see *Appendix 19*). We extracted detailed information on the components of interventions from studies of NP-guided treatment of heart failure identified in a systematic review[67,68] (see *Appendices 15* and *16*).

Detailed information on the interventions used in the studies was extracted from the papers in the review. We looked at univariate associations between components of the interventions and the strength of the reduction in the rate of heart failure hospitalisations and all-cause mortality. We compared intervention options in studies with significant and non-significant results to find components common to the more effective forms of the intervention.

We identified eight components across 10 studies that reported heart failure hospitalisation rates. The common-components analysis identified four components: a predefined treatment protocol, the locale of the heart failure clinic, setting a stringent NP target and incorporating a relative target as potential key components to reducing heart failure hospitalisations using NP-guided therapy.

The extent of what we could say about the effective components was limited by the number of studies that reported heart failure hospitalisations. Being unable to control for patient-level differences across studies may have masked the active components. Future studies should be conducted using individual patient data for their analyses.

Estimation of the variability of B-type natriuretic peptide and weight

To investigate variability in BNP concentrations and weight in patients with heart failure, we analysed data from the control arm of a RCT among patients with stable New York Heart Association (NYHA) class II or III CHF (see *Appendix 20*). The data were collected over 13 weeks of follow-up. Thirty patients in the control arm reported weight measurements weekly. BNP was measured every 6 weeks at 1, 7 and 13 weeks. The influence of age and obesity was investigated.

The between-person CV of weight was $< 26\%$ and of BNP was 137%. Between-person variation in BNP was higher for younger patients than for older patients with heart failure (the CV was 170% for age < 55 years and 88% for age ≥ 55 years), but did not appear to be related to obesity. Within-person variation was also substantial, but was smaller than between-person variation (the CV was 46% for BNP and 1.2% for weight).

The results suggest that monitoring over 3 months is unlikely to detect true BNP change against background noise in this small, chronically stable, heart failure population.

Feasibility study of the use of point-of-care natriuretic peptide testing in primary care

It has been postulated that routine monitoring of NP could assist in improving the care of patients with heart failure in the community.[70] Recent advances in technology provide the possibility of POC NP testing, but there is currently no evidence to support the use of such devices as part of routine care of patients with heart failure in primary care.

The primary aim of this study was to determine the variability in NP measurements made using POC NP technology in patients with heart failure in primary care settings, including both between- and within-person variability. Secondary outcomes assessing feasibility included the proportion of planned tests for which results were available (see *Appendix 21*).

We recruited adults with a recorded confirmed diagnosis of heart failure from three general practices in Oxfordshire between 20 February and 28 March 2018; follow-up was to 29 March 2019. Participants attended three scheduled visits at 0, 6 and 12 months from baseline. At all three visits, three venous blood samples were taken: one for POC NT-proBNP measurement (cobas® h 232 POC system; Roche Diagnostics, Rotkreuz, Switzerland), and two to be sent to the local laboratory for NT-proBNP and renal function testing.

Of 27 recruited participants, all attended visit 1, 23 attended visit 2 and 24 attended visit 3 (see *Appendix 21*). POC NT-proBNP measurements were successfully obtained at all visits attended by participants.

Within-person variability in POC NT-proBNP over 12 months was 881 pg/ml (95% CI 380 to 1382 pg/ml). Between-person variability was calculated using data from all 27 participants. Between-person variability in POC NT-proBNP over 12 months was 1972 pg/ml (95% CI 1525 to 2791 pg/ml).

We found that it was feasible to carry out POC NT-proBNP testing in primary care, with testing successfully carried out in 100% of planned study visits. However, no tests were carried out during routine primary care visits by the study participants. Between-person variability in POC NT-proBNP was around twice as large as within-person variability over 12 months. This would indicate that deviations from individual set points for NT-proBNP are likely to be more helpful than population-level thresholds when considering a monitoring strategy.

New qualitative evidence

Qualitative evaluation for chronic heart failure

To understand the acceptability and impact of current monitoring regimes in individuals with CHF, we used a mixture of patients' interviews and focus groups with health professionals (see *Appendix 9*). We used existing interviews conducted between 2003 and 2013, as well as new interviews focusing on monitoring. Participants for the focus groups with health professionals were recruited using a variety of methods, but were mainly drawn from practices from Oxfordshire and the wider Thames Valley area. Participant numbers for the focus groups were small, so the views expressed cannot be regarded as being representative of these professions.

Forty-three previously existing interviews and 16 new ones were analysed. The analysis aimed to focus on patients' attitudes to both the content and frequency of monitoring, adherence to and understanding of medications, and triggers of consultation. The analyses of the original and new interviews were published in (respectively) 2014 and 2016.[76] Sixteen health professionals participated in four focus groups: two consisting of community heart failure nurses (CHFNs), one of GPs and one of practice nurses.

A range of strategies was reported, with some people monitoring their weight and blood pressure at home, and some using TM. Monitoring could take place in either primary or secondary care (or both); care by specialist nurses was particularly valued. Frequency of check-ups ranged from yearly to weekly. Being monitored provided people with reassurance. A few expressed criticisms, which were minor, about their current regime, although, for some, titrating medication to optimal levels took too long. Advice about when to seek help did not seem to have been given other than for emergency situations. Approval for hypothetical future changes to monitoring regimens would be forthcoming, provided the rationale was explained. Increased reliance on blood testing in future would be acceptable, and POC testing in GPs' surgeries would be appreciated by people who would become anxious waiting days or weeks for test results.

As expected, CHF nurses were fully cognisant of the NICE guidelines for managing people with CHF, and used them daily to guide their care, with adjustment based on patient complexity (comorbidities).

GPs and practice nurses expressed unfamiliarity with the latest updates to NICE guidelines. NICE's website was considered confusing and difficult to navigate, and both GPs and practice nurses were more likely to learn about patient management recommendations from other sources, such as the Clinical Commissioning Group or QOF alerts. Given this, CHF nurses mentioned that they usually lead on treatment plans.

Chronic heart failure patients are regularly seen by practice nurses, but only as part of their management for other long-term conditions (driven by the QOF). GPs were unsure what tests they should be doing, and when and how to interpret and act on the results. Although they would welcome specific guidance from specialists about how to manage individual patients discharged from secondary care, they felt criticised by cardiologists for up-titrating a patient's medicines too slowly, when, in reality, this process could be challenging as a result of patient factors beyond their control.

Generally, both GPs and CHF nurses recognise NP as a useful diagnostic test for CHF, but CHF nurses could see no benefit of measuring NP as part of routine monitoring, instead suggesting that any changes in severity would be reflected in patients' symptoms. All groups believed that the cost of the test (both financial and in terms of professionals' time and extra blood samples required from the patient) would outweigh any potential benefits.

Economic issues

We aimed to identify health economic models used to address research questions related to monitoring heart failure in primary care, and hence to identify key issues. We reviewed the research questions addressed, the model structures and the data sources used to populate the models (see *Appendix 22*). A previous review by Goehler *et al.*[77] (including studies published be June 2010) was updated to August 2018 to identify analytical frameworks developed to evaluate heart failure interventions and management programmes in primary care. Studies were excluded if the research question was based fully within secondary care or if they reported local non-UK adaptations of already-included models.

Forty studies were identified: three focused on diagnosing heart failure, 11 focused on management strategies and 26 focused on drug interventions. Thirty-one studies used Markov model specifications with several different model structures. There was limited use of individual patient characteristics in the models. The data used to populate the parameters of the economic models were sourced predominantly from RCTs (undertaken several years ago) among patients with CHF recruited in hospitals.

Different models have been used to evaluate primary care interventions for patients with CHF. Despite the small number of studies that took into account patient characteristics, this appears to be increasing over time. Data from RCTs are widely used for estimating disease risks, quality-adjusted life-years (QALYs) and costs. Participants in these trials, frequently completed some years previously, were unlikely to be representative of the general CHF population in primary care. Future work should consider individual patient risk factors and include more recent data from CHF patients in primary care.

Three key issues were identified. First, the model structures were not generally sufficiently detailed to allow assessment of subtle improvements in disease monitoring. Second, a very small number of models accounted for individual patient characteristics and risks; however, this problem appears to be increasingly tackled in more recent models. Third, data to parameterise the economic models almost exclusively came from RCTs, many of which were completed some years previously and recruited patients exclusively in hospitals. Therefore, these data are unlikely to be representative of the target CHF population in primary care in the UK. Future work should consider individual patient risk factors and source more recent data from primary care.

Conclusions

This WS focused on management/monitoring of CHF in primary care, researching current practice and providing new evidence to guide this management. In particular, we concluded that:

- NP tests appear to be underused in primary care as part of diagnostic pathways (at least until 2013), which is not consistent with NICE guidance,[13] and are not used as part of a monitoring strategy (consistent with NICE guidance).
- NP-guided treatment might be beneficial in this population in reducing all-cause mortality and the rate of heart failure hospital admissions, although some uncertainty remains with regard to the size and robustness of this effect.
- We identified three components (plus being located in a specialist setting) that may be essential for NP-guided therapy in reducing the rate of heart failure hospitalisations – (1) using a predefined treatment protocol, (2) setting a stringent target and (3) the use of patient-specific targets.
- TM and STS in this population reduce the rate of all-cause mortality and hospital admission. Quality of life might also be improved by RM, although large levels of heterogeneity reduce our confidence in this beneficial effect.
- Within-person variability of BNP and weight is large, thereby reducing the chances of identifying true change in the condition using these measures.
- POC NP tests have variable ability to exclude CHF in patients in ambulatory care at low thresholds, but the ESC threshold for non-acute care for NT-proBNP might be an appropriate cut-off point for POC testing in this setting.
- It is feasible to carry out POC NT-proBNP testing in primary care, with testing successfully carried out in 100% of planned study visits. However, no opportunistic tests were conducted.
- Between-person variability in POC NT-proBNP is around twice as large as within-person variability over 12 months.
- Professionals consider the use of NP tests for monitoring expensive, of limited benefit and, potentially, a waste of scarce resources.
- Health economic studies increasingly consider individual patient factors, but are limited by a lack of data from CHF patients typically seen in primary care.

Research recommendations

- Further studies evaluating the efficacy of NP-guided treatment in CHF are needed. Based on a 13% relative reduction from a 15% mortality (baseline), an excess of 10,000 participants will be required to have a sufficiently powered ($\geq$ 80%) study. Current systematic reviews/meta-analyses include just over 4000 participants.
- Any such studies should collect resource data on length of hospital stay and re-admission rates, which are critical for the health service and will facilitate assessment of cost-effectiveness.
- The potential mechanisms for an effect on mortality, such as increased patient and physician adherence to treatment regimens, should be explored.
- New and ongoing studies of RM need to be incorporated promptly to systematic reviews; these should consider changes in the technologies used for this purpose.
- Determining the appropriate threshold for the use of POC NP testing is needed if this technology is to be incorporated as part of a diagnostic or monitoring pathway.
- Exploring the barriers to the routine use of NP and POC NP testing is needed to increase health practitioners' use of these tests.
- More detailed data on sociodemographic and clinical characteristics, including disease progression and health-care use, from CHF patient cohorts in primary care are required to inform assessments of monitoring strategies.

Implications for practice

- If NP tests are not currently used as part a diagnostic pathway in primary care, which goes against the NICE recommendation, their use could be incentivised.
- RM, using either TM or STS, in the care of CHF should be considered, as it is likely to reduce the rates of all-cause mortality and heart failure hospital admissions, and may improve quality of life.
- NP tests have variable ability to exclude CHF in patients in ambulatory care at low thresholds, but the ESC threshold for non-acute care for NT-proBNP might be an appropriate cut-off point for POC testing in this setting.
- As between-person variability in POC NT-proBNP was around twice as large as within-person variability over 12 months, this indicates that deviations from individual targets for NT-proBNP are likely to be more helpful than population-level thresholds when considering a monitoring strategy.
- Both NP and weight are highly variable measures; therefore, any change observed should be interpreted with caution.
- Use of POC tests to measure NP in general practice is feasible, but does not lead to reductions in observed variability.
- There are substantial barriers to the implementation of NP-guided treatment in primary care. In particular, the perception from health practitioners, both nurses and clinicians, is that the use of NP measures may not be beneficial.

Reflections

Pharmacological treatments for heart failure in primary care are well established, but must be managed (titrated) with great care and may temporarily worsen patient quality of life. This may contribute to the major underuse of evidence-based therapies in routine practice, which may, in turn, increase the likelihood of urgent admissions with worsening heart failure. Identifying ways of detecting heart failure deterioration is therefore likely to be important for patients and health-care systems. There is, therefore, strong prima facie evidence for a role for monitoring, but we find that the candidate monitoring measures – NP, and also weight – have relatively high within-measurement variability. In this context, it is perhaps not surprising that we find encouraging, but inconsistent, evidence from trials that monitoring to guide treatment, by clinicians or at home, is potentially life-saving. Future research should investigate the settings and methods in which monitoring has the most benefit, and we suggest that refining the reliability of measurements, whether through new biochemical methods or through averaging several measurements to reduce noise, is a promising direction in which to start.

Patient and public involvement

Background

The target audiences for this programme of research were patients/the public and health practitioners, so a stakeholder group was formed comprising these two groups. We planned to include PPI representatives (6/12), nurse practitioners (3/12), pharmacists (1/12) and clinicians (2/12). The group's tasks included providing views on the plans for design, implementation and evaluation of monitoring strategies; participating in developing the plans for understanding patient and GP factors associated with monitoring; contributing to plans to explore the views of patients and practitioners of potential changes to the type of test used, frequency of testing and setting of testing; guiding and advising on the dissemination of individual research projects in the programme; and providing representation on the steering group. Two members joined the steering group: one PPI member and one clinician. PPI members were offered remuneration for their time and travel expenses. However, not all PPI members claimed any or all of the offered expenses. Training and support for PPI members were available and were provided by the Nuffield Department of Primary Care Health Sciences. The group met regularly, every 6 months, throughout the duration of the programme, with the principal investigator (PI), deputy PIs and the programme managers. Agendas were prepared and sent in advance, together with relevant paperwork, via e-mail. Any member of the stakeholder group could suggest changes and additions to the agenda. The PI chaired these meetings, while the programme managers took minutes, which were circulated to all members, usually within 1 month of the meeting. Views and opinions from the group were collected during the meetings, but were also accepted via e-mail, particularly when members were not able to attend in person. The terms of reference for this group are in *Appendix 23*.

Processes and contributions

We held seven face-to-face meetings and one teleconference. For all face-to-face meetings, teleconference facilities were available, although they were used infrequently. All meetings lasted for between 1 and 2 hours. Once per year (on four occasions), the stakeholder group was invited to also attend the senior management meetings and research presentations to help with the dissemination of the findings. Finally, in April 2019 we held a dissemination day for the stakeholder group that lasted 5.5 hours (including lunch).

As the programme lasted for > 5 years, the membership of the stakeholder group changed, but some members (notably four of the PPI contributors) remained throughout the grant. Overall, during the term of the programme, a total of 15 members contributed: seven patients or lay representatives; two primary care nurses, four GPs, one pharmacist and one heart failure nurse from secondary care.

Working practices between the stakeholder group and the research team were a collaborative undertaking. Communications were established and maintained to ensure that the stakeholder group was fully informed of the research projects, at all stages. In accordance with the terms of reference, the stakeholder group assisted the research team in five main areas: (1) designing and conducting the primary quantitative research projects (FORM-2C and feasibility of POC BNP testing in monitoring), (2) planning qualitative research in current monitoring, (3) planning qualitative research on potential changes in monitoring regimes, (4) guiding and advising on the dissemination of research and (5) representing the stakeholders on the steering group for the programme.

The stakeholders were instrumental in helping the research team design the quantitative primary research studies and were involved in the very earliest stages of development, before seeking ethics approval.

Examples of the influence that the group (principally the patient and lay members) had on the design and execution of the research are as follows: for FORM-2C, the group designed a schedule of visits that it felt could be incorporated into regular visits to the doctor's surgery and the development of the patient information materials. In the POC feasibility study, it again advised us about the development of the protocol.

For the qualitative components of the programme, the stakeholder group commented on the draft interview guides for CHF projects and specifically considered whether or not it covered all relevant aspects, whether or not the language was appropriate, and how onerous the interview might be for people with heart failure (is it overambitious?). The group was also asked to suggest proposed sampling categories. One member helped with recruitment. The group also commented on the published https://healthtalk.org/ (accessed 5 May 2020) site, particularly concerning the CKD interviews.

The research team developed a few short audio/Microsoft PowerPoint® (Microsoft Corporation, Redmond, WA, USA) presentations to show during the focus groups with health professionals, to trigger discussion. The stakeholder group commented on these presentations, which were then modified accordingly. They also provided feedback on the study results.

As the programme progressed, we discussed the methodological approaches taken, and the stakeholder group provided comments. At one point, it queried whether or not we were analysing the most appropriate data in a project,[23] as we were not analysing rates of renal testing using cystatin C. The group was familiar with cystatin C as a serum marker of kidney function, as it is the alternative marker used in the FORM-2C project. We were able to clarify that, at that time, cystatin C was not routinely used in clinical practice. However, had this been an oversight, this would have been identified.

A recurrent theme during the programme was feedback regarding terminology, such as the use of the label CKD, with the term 'disease' being considered as frightening. The interviews conducted as part of the qualitative evaluation for CKD alerted some stakeholder members to the reluctance of GPs to tell patients about CKD, and patients' confusions over the terminology of CKD ultimately led to a spin-off project, Kidney Age[45] (see *Appendix 11*). This, in turn, has been the foundation of small, additionally funded, projects to develop patient and health professional communication resources to enhance discussions about kidney health and ageing. The stakeholder group was very influential in this work, discussing the terminology that is currently used, developing a patient-facing information sheet and helping devise the methodological approach to evaluate the potential usefulness of such a resource. It felt that this research was vital to provide signposting and communication for patients, as providing clear information can relieve anxiety.

Once individual projects started to produce outputs, the stakeholder group provided editorial and content comments on lay summaries for the paper by Taylor *et al.*[74] (see *Appendix 18*) and the plain language summary for the paper by McLellan *et al.*[67] (see *Appendix 15*), and gave comments on drafted manuscripts for most projects.

Potential mechanisms to disseminate the findings of the programme were discussed. Suggestions included via The Kidney Alliance, the Nuffield Department of Primary Care Health Sciences PPI newsletter, the GP magazine *Pulse* and the knowledge summaries on the NICE website.

Stakeholder group's reflections on the findings and implications for NHS and funders

Towards the end of the period of funding, we held an internal dissemination meeting attended by five members of the stakeholder group. A senior qualitative researcher with a particular interest in PPI facilitated this meeting.

The stakeholder members were supportive of the research approaches that we had taken and reported that they found the results interesting and congruent with their experiences, views and beliefs. Overall, they felt that the generalisability of the research was good, and saw it as delivering benefit to research and patients.

They felt that the results serve to add to the case for NHS England to continue to support and encourage evidence-based practices throughout the NHS, especially in the light of the benefits to patients and the potential for funding to be saved. The results also suggest that consistency in the use of evidence-based treatments across all 44 NHS integrated care systems would benefit patients across England driving down inequalities in health care provision. Regarding research funding, it was felt that the results emphasised the importance of continuing to fund ongoing research into wide-ranging aspects of current clinical care practices, for both patient benefit and achieving value for money.

Lessons learnt on the role and impact of patient and public involvement: reflections from members of the stakeholder group

Members of the stakeholder group reflected on their experiences of participating in this programme, and felt that it had been well organised, with good administration, communication and paperwork. They felt that PPI contributors were treated with every consideration and that their needs were very well catered for in all respects. They felt appreciated, valued, accepted and included as part of the team. One member commented that they liked that the senior staff always attended the meetings, not just more junior researchers in the team. Members reported that their experience in this programme was better than in previous PPI groups, with one participant saying that they felt that, when PPI was first introduced, it was actually held in contempt, even more so because participants tended to be older, and older people were held in contempt too. However, the whole concept of PPI has been moving forward over the years and the participants who attended the dissemination event uniformly had an enjoyable and beneficial experience that exceeded their expectations.

One participant reported that they would have valued greater clarity on what to expect at the beginning, such as the time taken and demands. They were told you ‘can do as much as you want’, but, as a numbers person, they felt that this did not help. They would have appreciated a ‘job description’. Partly in response to this comment, and incorporating suggestions from this participant, the Nuffield Department of Primary Care Health Sciences PPI co-ordinator has subsequently produced guidance for PPI members on future projects. Another member commented that the concurrent training programme for PPI contributors was also a helpful adjunct to those involved in the programme. As a result, the experience of being a PPI contributor to this programme was very positive, especially feeling that, as a layperson, and in a relatively small way, they had been able to contribute to this important piece of work.

Regarding the practicalities of attending meetings, all the attendees preferred the face-to-face meetings; in fact, they would have complained or not participated if many of the meetings had been carried out by teleconference. Covering travelling costs and having lunches were seen as important to ongoing engagement.

Lessons learnt: reflections of the research team

The research team found it easier to recruit to the CKD streams than to the heart failure stream. The patient and lay participants who withdrew during the term of the programme did so because of deteriorating health, although, at times, they contributed via telephone or e-mail, as that was manageable with their health condition. Initially, at the start of the programme, the balance of the stakeholder group was more towards the health professionals than the public, although, over time,

several of the health professionals dropped out because of work commitments. During the second half of the programme, the stakeholder group principally constituted patient and lay members.

Regarding how best to incorporate PPI, we feel that, although, for some projects (specifically FORM-2C), PPI was initiated at the design stage, a clearer strategy for when PPI could be included could have been developed. A projected overview of what, when and how PPI would be needed for each project would have made the process run even smoother. At times, it felt that we were looking for places to include PPI. However, perhaps this ebbing and flowing of the need for involvement of any type of participant (PPI, statistician, clinician) is an inherent part of the research process, in that it differs according to the stage of the research. This is a reflection too on the nature of the projects in the WSs: much of our research has been systematic reviews and methodological work, and maybe it is easier to see a role for PPI in primary research that has direct participant involvement than in research using routine or previously collected data.

Overall conclusions

Management of chronic disease requires monitoring, almost by definition. CKD is an example of a condition for which monitoring measures the progression of disease to manage long-term risk, whereas CHF is an example of a condition for which monitoring has been suggested as being important for guiding treatment.

In some chronic conditions, randomised trials have been conducted of monitoring either as an intervention in its own right or as a component of a management strategy. For example, multiple randomised trials of monitoring have been conducted in hypertension[78] and diabetes,[79] but these trials usually use surrogate outcome measures such as blood pressure or HbA_{1c}, instead of hard outcomes such as CVD. Evaluation of medical testing against hard outcomes usually requires modelling, rather than randomised trials.[80]

For each of the two exemplar conditions, we began by reviewing current practice. For CKD, monitoring based on blood tests and urine testing is widespread, accounting for millions of tests in the NHS each year. For CHF, blood tests such as NP are available, but are currently little used.

Mant[81] suggested that the following minimum criteria should be in place for a monitoring strategy to be justifiable. First, it is necessary that 'clinically significant changes in the condition . . . occur over time'.[81] For CKD and CHF, the time scales differ, but changes in condition can be highly clinically significant.

Second, there must be 'an available monitoring test that reliably detects clinically significant changes when they occur'.[81] We studied the properties of blood tests for CKD, and of BNP and weight as monitoring tests for CHF. For CKD, we found that different blood tests and different equations are similarly useful for estimating GFR. For CHF, we found a range of devices available for testing NP at the POC, but no clear evidence on which device may be the best for use in practice. For both CKD and CHF, we found that blood tests (serum creatinine and NP, respectively) have non-trivial measurement error, that is that the within-person or within-measurement variation is not small, compared with the between-person variation and rate of change. This implies that any monitoring strategy that is sensitive to changes may not be specific, and, in the case of CKD, we quantified this, showing that most of the observed changes in CKD stage are due to misclassification. This is consistent with previous studies of monitoring conditions such as hypertension, dyslipidaemia, diabetes and diabetic kidney disease in primary care.[7,9,10,82] In all these conditions, monitoring programmes are likely to detect many apparent changes in condition due to measurement variability, and this problem is exacerbated by frequency of monitoring.[6]

Third, 'cost-effective action can be taken on the basis of the test result'.[81] We conducted systematic reviews of available actions in both chronic conditions. For CKD, we found evidence that some glucose-lowering and lipid-modifying interventions, in particular, may be beneficial to slow the progress of CKD, as well as reduce the risk of other conditions. For CHF, we found gaps in the current evidence for monitoring and management interventions as a whole, but there are established pharmacological therapies, including ACE inhibitors, ARBs, beta blockers, mineralocorticoid receptor antagonists, diuretics or aldosterone antagonists, for reducing risk and improving life expectancy[16] in people living with CHF.

For both CKD and CHF, whether or not the available actions are cost-effective is more difficult to determine. Our cost-effectiveness model of CKD found minimal evidence to support monitoring in the early stages of CKD, with most patients already eligible for the treatments that may be indicated, making it difficult to justify monitoring in the scheme proposed by Mant.[81] For heart failure, cost-effectiveness of the treatments is established,[77] but cost-effectiveness of monitoring as a whole is

harder to establish because of other evidence gaps, for primary care populations in particular, as most evidence available does not include this population.

Thus, for both conditions, although our qualitative work and feasibility study demonstrate the acceptability and potential usefulness of monitoring, there are substantial gaps in the evidence to demonstrate that monitoring is cost-effective. In CKD, the main evidence gap is for an action to be taken, in response to worsening CKD, which would not already be in place for most patients anyway. In CHF, evidence-based treatments are established but there is no proven reliable test for monitoring (e.g. large variability of NPs and weight).

Limitations

We did not attempt to produce RCT evidence, which has both challenges and limitations for monitoring strategies,[80] but we did systematically review existing trials of CHF monitoring. For CKD, we systematically reviewed and synthesised RCT evidence for treatments because, as discussed previously, one of the minimum criterion for monitoring to be beneficial is the existence of an action that can usefully be taken when monitoring detects change. Limitations of individual projects are discussed elsewhere in this document [Oke *et al.*[22] (see *Appendix 2*); Feakins *et al.*[23] (see *Appendix 3*); McFadden *et al.*[24] (see *Appendix 5*); Taylor *et al.*[25] (see *Appendix 6*); Oke *et al.*[26] (see *Appendix 7*); prospective cohort study of monitoring CKD (FORM-2C) (see *Appendix 8*); qualitative evaluation for CKD[30] (see *Appendices 9* and *10*); review of economic models (see *Appendix 12*); cost-effectiveness of monitoring kidney function in UK primary care[38] (see *Appendix 14*); McLellan *et al.*[67,68] (see *Appendices 15* and *16*); remote monitoring, telemonitoring and structured telephone support to monitor heart failure (see *Appendix 17*); Taylor *et al.*[74] (see *Appendix 18*); Oke *et al.*[75] (see *Appendix 19*); estimation of the variability of BNP and weight (see *Appendix 20*); feasibility study of use of POC NP tests in primary care (see *Appendix 21*); qualitative evaluation for CHF (see *Appendix 9*); and economic issues (see *Appendix 22*)]. Here, we call attention in particular to the limitation of our CKD WS: that the benefits of (e.g. annual) monitoring are difficult to quantify in the absence of a quantifiable, evidence-based, pathway to follow when monitoring detects deterioration. We have advanced knowledge about the reliability of NP and weight in the management of CHF. Given the size of the variability of each of these measures, the only situations in which either would prove useful would be if the signal detected was substantially larger or the noise could be minimised. This programme has not evaluated whether or not such clinical situations or measurement strategies could exist.

All publications from this programme of research are listed in *Publications*.

Acknowledgements

We would like to thank the following colleagues, clinicians, patients and public for their help and support in this research programme:

- Philip Alderson, Research synthesis, NICE (Steering Committee).
- Julie Barker, Research and Development Manager, Oxfordshire Clinical Commissioning Group.
- Kristina Bennert, Research Associate (contributed to qualitative interviews).
- John Burden (PPI).
- Alison Clements, Senior Qualitative Researcher (contributed to essential components in NP-guided management of heart failure).
- Kiren Collison, Clinical Chair of the Oxfordshire Clinical Commissioning Group (stakeholder group).
- Di Croft (stakeholder).
- Robert Cummings (PPI, Steering Committee).
- Andrew Farmer, Professor of General Practice, Nuffield Department of Primary Care Health Sciences (contributed to application of the programme grant).
- Robin Ferner, Professor of Clinical Pharmacology (Steering Committee).
- Natasha Francis (PPI).
- Alice Fuller, Research Officer (data management).
- Laura Hill (stakeholder group).
- Elizabeth Holloway (PPI).
- Jade Howard, Research Assistant for the Health Experiences Research Group (contributed to qualitative focus groups).
- Jeremy Horwood, Senior Research Fellow in Ethnography/Qualitative Social Science (contributed to qualitative interviews and analysis).
- Jennifer A Hirst, Senior Primary Care Researcher (contributed to systematic review of GFR equation comparability).
- Tim James, Laboratory Manager (laboratory tests).
- Marion Judd (PPI).
- Peter Kirby (PPI).
- Emily C McFadden, Senior Statistical Epidemiologist (data manager and systematic review of GFR equation comparability).
- Joanne Noble, Community Heart Failure Nurse (contributed to feasibility study of POC NP monitoring in patients with heart failure in primary care).
- Mercia Page (Steering Committee).
- Frank Palma (PPI).
- Rachael Patel (PPI).
- Christopher Price, Visiting Professor in Clinical Biochemistry (contributed to diagnostic accuracy POC NP testing for CHF in ambulatory care).
- Kristy Ravenhall, Administration Assistant (data entry).
- Oliver Rivero-Arias, Professor in Health Economics (contributed to the application of the programme grant).
- Mary Selwood, Research Nurse/Study Manager (former lead to the observational cohort study for primary care patients with reduced eGFR).
- Debs Smith (PPI).
- Matthew Thompson, Professor of Family Medicine (contributed to the application of the programme grant).
- David Timmins, FORM-2C Project Manager (contributed to the observational cohort study for primary care patients with reduced eGFR).
- Sula Wiltshire, Associate Director of Quality at Oxfordshire Clinical Commissioning Group.

The observational cohort study for primary care patients with reduced eGFR and the feasibility study of the use of POC NP monitoring in patients with heart failure in primary care would not have been possible without the help of the participating patients. We would like to thank the following general practices and their practice nurses for their participation and co-operation with this study: Bicester Health Centre (Emily Ackland and Claire Giles), Didcot Health Centre (Ruth Atkinson and Sarah Hyner), Observatory Medical Practice (Kathryn Balmford and Antonia Michalikova), Summertown Health Centre (Mandy Beckett, Wendy Cubiss and Sam Towers), Botley Medical Centre (Liz Burquest), Westongrove Research Centre (Paula Caldwell), Gosford Hill Medical Centre (Sam Davies), Islip Medical Practice (Debbie Denton), Woodlands Medical Centre (Angela Fountain), The Boathouse Surgery (Wioletta Kowalczyk-Williams), Woodlands Medical Centre (Sue Paton and Jackie Peck), Eynsham Medical Group (Leanda Rankin and Janice Williams), Broadshires Health Centre (Sarah Sanders), White Horse Medical Practice (Debbie Warwick) and Berinsfield Health Centre (Sarah Williams). In addition, we would like to acknowledge the support of the National Institute for Health Research Clinical Research Network.

Contributions of authors

Professor Rafael Perera (https://orcid.org/0000-0003-2418-2091) (PI, Director of Medical Statistics) designed, interpreted data for and prepared for publication the study of local variation of practice (Oxford) data;[22] conducted all aspects of the study of national variations in practice – CPRD data; designed and prepared for publication the systematic review of interventions for CKD stages G3 and G4; designed, interpreted data for and prepared for publication the estimation of variability of eGFR; designed, analysed, interpreted data for and prepared for publication the prospective cohort study of monitoring CKD (FORM-2C); conducted all aspects of the evaluation of intervention components; conducted the systematic review of BNP-guided treatment for heart failure; prepared for publication the systematic review of RM of CHF; designed and prepared for publication the systematic review of the diagnostic accuracy of POC devices; conducted all aspects of the estimation of variability of BNP and weight; and designed and prepared for publication the feasibility study of use of POC BNP testing in primary care.

Professor Richard Stevens (https://orcid.org/0000-0002-9258-4060) (Deputy PI, Deputy Director of Medical Statistics) interpreted data for and prepared for publication the study of local variation of practice (Oxford) data; conducted all aspects of the study of national variations in practice – CPRD data; designed, analysed, interpreted data for and prepared for publication the systematic review of GFR equation comparability; prepared for publication the systematic review of economic models of CKD; prepared for publication the systematic review of interventions for CKD stages G3 and G4; designed and prepared for publication the estimation of variability of eGFR; designed, interpreted data for and prepared for publication the prospective cohort study of monitoring CKD (FORM-2C); prepared for publication the qualitative evaluation of monitoring CKD; prepared for publication the cost-effectiveness model of strategies for CKD; prepared for publication the estimation of variability of BNP and weight; prepared for publication the feasibility study of use of POC BNP testing in primary care; and prepared for publication the systematic review of economic models of CHF.

Professor Jeffrey K Aronson (https://orcid.org/0000-0003-1139-655X) (Consultant Physician and Clinical Pharmacologist, pharmacology) designed, interpreted data for and prepared for publication the study of national variations in practice – CPRD data;[23] and designed, interpreted data for and prepared for publication the systematic review of interventions for CKD stages G3 and G4.

Professor Amitava Banerjee (https://orcid.org/0000-0001-8741-3411) (Senior Lecturer in Clinical Data Science and Honorary Consultant in Cardiology, heart failure service, cardiac services) designed, analysed and prepared for publication the study of the evaluation of intervention components; designed and prepared for publication the estimation of variability of BNP and weight; designed and prepared for publication the feasibility study of use of POC BNP testing in primary care; designed the qualitative evaluation of monitoring CHF; and designed, interpreted data for and prepared for publication the systematic review of economic models of CHF.

Dr Julie Evans (Senior Researcher) conducted all aspects of the qualitative evaluation of monitoring CKD and conducted the qualitative evaluation of monitoring CHF.

Dr Benjamin G Feakins (https://orcid.org/0000-0002-3928-6750) (Statistician, Epidemiologist) conducted all aspects of the study for national variations in practice – CPRD data.

Dr Susannah Fleming (https://orcid.org/0000-0001-7205-2051) (Senior Qualitative Researcher, monitoring and diagnosis) analysed, interpreted data for and prepared for publication the systematic review of interventions for CKD stages G3 and G4; conducted all aspects of the prospective cohort study of monitoring CKD (FORM-2C); and conducted the feasibility study of use of POC BNP testing in primary care.

Professor Paul Glasziou (https://orcid.org/0000-0001-7564-073X) (Director of the Institute for Evidence Based Healthcare, evidence-based medicine) designed, analysed and interpreted data for the evaluation of intervention components, and conducted the systematic review of BNP-guided treatment for heart failure.

Professor Carl Heneghan (https://orcid.org/0000-0002-1009-1992) (Director of the Centre for Evidence-Based Medicine and Programs in Evidence-Based Health Care, epidemiologist) designed, analysed and prepared for publication the systematic review of BNP-guided treatment for heart failure; designed the estimation of variability of BNP and weight; and designed the systematic review of economic models of CHF.

Professor FD Richard Hobbs (https://orcid.org/0000-0001-7976-7172) (Head of Nuffield Department of Primary Care Health Sciences, Senior Researcher in cardiovascular epidemiology and clinical trials) designed, interpreted data for and prepared for publication the systematic review of GFR equation comparability; designed, interpreted data for and prepared for publication the systematic review of interventions for CKD stages G3 and G4; interpreted data for and prepared for publication the study of estimation of variability of eGFR; designed and prepared for publication the prospective cohort study of monitoring CKD (FORM-2C); designed and prepared for publication the study of estimation of variability of BNP and weight; and designed and prepared for publication the feasibility study of use of POC BNP testing in primary care.

Dr Louise Jones (https://orcid.org/0000-0002-0519-2334) (Clinical Trials Manager, health-care research) conducted the prospective cohort study of monitoring CKD (FORM-2C).

Dr Milena Kurtinecz (https://orcid.org/0000-0001-6869-5628) (Clinical Researcher, evidence-based medicine) conducted all aspects of the study for estimation of variability of BNP and weight.

Professor Daniel S Lasserson (https://orcid.org/0000-0001-8274-5580) (Professor of Ambulatory Care, acute medical care) designed, analysed and prepared for publication the study of local variation of practice (Oxford) data; conducted all aspects of the systematic review of GFR equation comparability; designed, interpreted data for and prepared for publication the systematic review of economic models of CKD; designed, analysed and prepared for publication the systematic review of interventions for CKD stages G3 and G4; designed the work for the estimation of variability of eGFR; designed and prepared for publication the prospective cohort study of monitoring CKD (FORM-2C); and designed and prepared for publication the cost-effectiveness model of strategies for CKD.

Professor Louise Locock (https://orcid.org/0000-0002-8109-1930) (Professor in Health Services Research Unit, Qualitative Social Science Researcher) conducted all aspects of the qualitative evaluation of monitoring CKD and conducted the qualitative evaluation of monitoring CHF.

Mrs Julie McLellan (https://orcid.org/0000-0002-2868-8631) (Programme Manager and Research Officer, systematic reviews) analysed, interpreted data for and prepared for publication the systematic review of GFR equation comparability; conducted all aspects of the systematic review of interventions for CKD stages G3 and G4; analysed, interpreted data for and prepared for publication the evaluation of intervention components; analysed, interpreted data for and prepared for publication the systematic review of BNP-guided treatment for heart failure; and conducted all aspects of the systematic review of RM of CHF.

Professor Borislava Mihaylova (https://orcid.org/0000-0002-0951-1304) (Senior Health Economist, economic aspects of chronic disease) designed, analysed and prepared for publication the systematic review of economic models of CKD; interpreted data for the systematic review of interventions for CKD stages G3 and G4; designed and prepared for publication estimation of variability of eGFR; conducted all aspects of the cost-effectiveness model of strategies for CKD; and conducted all aspects of the systematic review of economic models of CHF.

Professor Christopher A O'Callaghan (https://orcid.org/0000-0001-9962-3248) (Professor of Medicine, bioinformatics, statistics and computational biology), designed and prepared for publication the study of local variation of practice (Oxford) data; prepared for publication the study of national variations in practice – CPRD data; designed and prepared for publication the systematic review of GFR equation comparability; designed and prepared for publication the systematic review of interventions for CKD stages G3 and G4; designed and prepared for publication the estimation of variability of eGFR; designed and prepared for publication the prospective cohort study of monitoring CKD (FORM-2C); and designed and prepared for publication the cost-effectiveness model of strategies for CKD.

Dr Jason L Oke (https://orcid.org/0000-0003-3467-6677) (Senior Statistician, overdiagnosis and overtreatment), analysed, interpreted data and prepared for publication the study of local variation of practice (Oxford) data; analysed, interpreted data and prepared for publication the study of national variations in practice – CPRD data; analysed, interpreted data for and prepared for publication the estimation of variability of eGFR; and analysed, interpreted data for and prepared for publication the evaluation of intervention components.

Ms Nicola Pidduck (https://orcid.org/0000-0002-6491-1159) (Programme Manager and Researcher, systematic reviews) interpreted data for and prepared for publication the systematic review of interventions for CKD stages G3 and G4; interpreted data for and prepared for publication the systematic review of BNP-guided treatment for heart failure; and designed, interpreted data for and prepared for publication the systematic review of RM for CHF.

Dr Annette Plüddemann (https://orcid.org/0000-0003-2101-0390) (Course Director of the MSc in Evidence-Based Health Care and Senior Research Fellow, evidence-based medicine) conducted all aspects of the systematic review of the diagnostic accuracy of POC devices.

Ms Nia Roberts (https://orcid.org/0000-0002-1142-6440) (Librarian, research and clinical care) designed and prepared for publication the systematic review of interventions for CKD stages G3 and G4, and designed and prepared for publication the systematic review of BNP-guided treatment for heart failure. She also completed the updated publication search for the systematic review, remote monitoring, telemonitoring and structured telephone support to monitor heart failure.

Dr Iryna Schlackow (https://orcid.org/0000-0002-4154-1431) (Senior Researcher, economics in CKD and CVD) conducted all aspects of the systematic review of economic models of CKD; analysed, interpreted data for and prepared for publication estimation of variability of eGFR; and conducted all aspects of the cost-effectiveness model of strategies for CKD.

Dr Brian Shine (https://orcid.org/0000-0002-1016-8638) (Consultant Chemical Pathologist, endocrinology and diabetes) conducted all aspects of the study of local variation of practice (Oxford) data, and designed and prepared for publication the feasibility study of use of POC BNP testing in primary care.

Dr Claire L Simons (https://orcid.org/0000-0003-0822-7261) (Senior Researcher), interpreted data and reviewed content for estimation of variability of eGFR; analysed, interpreted data for and prepared for publication the cost-effectiveness model of strategies for CKD; and conducted all aspects of the systematic review of economic models of CHF.

Dr Clare J Taylor (https://orcid.org/0000-0001-8926-2581) (National Institute for Health Research Academic Clinical Lecturer, heart failure) interpreted data for and prepared for publication the study of national variations in practice (Oxford) data; interpreted data for and prepared for publication the evaluation of intervention components; interpreted data for and prepared for publication the systematic review of home-monitoring for CHF; conducted all aspects of the feasibility study of use of POC BNP testing in primary care; and interpreted data for and prepared for publication the systematic review of economic models of CHF.

Dr Kathryn S Taylor (https://orcid.org/0000-0001-6589-5456) (Medical Statistician, systematic reviews and meta-analysis) conducted all aspects of the systematic review of economic models of CHF; analysed, interpreted data for and prepared for publication the prospective cohort study of monitoring CKD (FORM-2C); analysed, interpreted data for and prepared for publication the systematic review of home-monitoring for CHF; and interpreted data for the systematic review of the diagnostic accuracy of POC devices.

Dr Jan Y Verbakel (https://orcid.org/0000-0002-7166-7211) (Clinical Researcher, diagnosis of serious diseases in primary care) designed, interpreted data for and prepared for publication the systematic review of interventions for CKD stages G3 and G4, and interpreted data for and prepared for publication the systematic review of the diagnostic accuracy of POC devices.

Professor Clare Bankhead (https://orcid.org/0000-0003-1588-3849) (Deputy PI, Senior Researcher) designed the study of national variations in practice (Oxford) data; designed and analysed the systematic review of GFR equation comparability; designed, analysed, interpreted data for and prepared for publication the systematic review of interventions for CKD stages G3 and G4; conducted all aspects of the prospective cohort study of monitoring CKD (FORM-2C); designed the qualitative evaluation of monitoring CKD; conducted the evaluation of intervention components; conducted all aspects of the systematic review of BNP-guided treatment for heart failure; conducted the systematic review of the diagnostic accuracy of POC devices; designed and analysed the feasibility study of use of POC BNP testing in primary care; and designed the qualitative evaluation of monitoring CHF.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Chronic kidney disease by glomerular filtration rate and albuminuria stages

				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30–300 mg/g 3–30 mg/mmol	> 300 mg/g > 30 mg/mmol
GFR categories (ml/min/1.73 m^2) Description and range	G1	Normal or high	≥ 90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	< 15			

FIGURE 2 Prognosis of CKD by GFR and albuminuria category. Albuminuria = proteinuria. Light blue: low risk (if no other markers of disease, no CKD); purple: moderately increased risk; mid-blue: high risk; orange: very high risk. Reprinted from *Kidney International*, Vol. 80, Levey AS, de Jong PE, Coresh J, Nahas MEI, Astor BC, Kunihiro Matsushita K, *et al.*[83] The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report, Copyright 2011, with permission from Elsevier.

Based on NICE guidance[11] from 2014 (updated in January 2015 and checked by NICE in April 2017; due to be updated by 30 June 2021[84]), the following monitoring schedule is recommended:

- ≤ 1 per year: G1/A1 and G2/A1
- 1 per year: G1/A2, G2/A2, G3a/A1 and G3a/A2
- ≥ 1 per year: G1/A3 and G2/A3
- ≤ 2 per year: G3b/A1
- 2 per year: G3a/A3, G3b/A2, G4/A1, and G4/A2
- ≥ 2 per year: G3b/A3
- 3 per year: G4/A3
- 4 per year: G5/A1
- ≥ 4 per year: G5/A2 and G5/A3.

Appendix 2 Trends in serum creatinine testing in Oxfordshire, UK, 1993–2013: a population-based cohort study

Oke *et al.*[22] https://doi.org/10.1136/bmjopen-2015-009459

Appendix 3 Trends in kidney function testing in UK primary care since the introduction of the quality and outcomes framework: a retrospective cohort study using the Clinical Practice Research Datalink

Feakins *et al.*[23] https://doi.org/10.1136/bmjopen-2018-028062

Appendix 4 Protocols for research using the Clinical Practice Research Datalink

This appendix contains a quotation from NICE.[85] © NICE 2008 *Chronic Kidney Disease: Early Identification and Management of Chronic Kidney Disease in Adults in Primary and Secondary Care*. Available from www.nice.org.uk/guidance/CG73 All rights reserved. Subject to Notice of rights. The NICE guidance is prepared for the NHS in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this product/publication.

Figure 1 is reprinted from *Kidney International*, Vol. 80, Levey AS, de Jong PE, Coresh J, Nahas MEI, Astor BC, Kunihiro Matsushita K, *et al.*[83] The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report, Copyright 2011, with permission from Elsevier.

Monitoring kidney function in primary care: an overview of current practice and identification of optimal strategies

Summary of Research in plain English

Monitoring of kidney function in primary care is important for two main reasons. Firstly, to diagnose chronic kidney disease especially in patients with conditions, such as diabetes or heart failure, which may affect their kidney function; secondly, to determine when to refer patients with existing kidney disease to specialist assessment such as if their kidney function becomes very poor or declines very quickly. Disease progression can be delayed if it is identified early.

Kidney function is usually tested through blood or urine tests. We would like to use the Clinical Practice Research Datalink (CPRD) to describe how many of these tests are carried out in usual practice in the UK, how many are used for initial diagnosis of kidney disease or for monitoring of existing disease, and to examine whether testing varies by region, calendar-period or the existence of major long-term conditions, such as heart disease, high blood pressure or diabetes.

As current national guidelines for how frequently patients should be tested are based on low-quality evidence, we would also like to use the CPRD to model different monitoring scenarios to identify the best strategy for testing, and to make recommendations on how often testing should occur for diagnosis and monitoring purposes.

Background and rationale

Chronic Kidney Disease (CKD) is a largely asymptomatic condition where kidney function and/or structure is abnormal (1,2). About 2 million adults in England have been diagnosed

with moderate to severe CKD, defined by persistent proteinuria or estimates of reduced glomerular filtration rate from serum creatinine (eGFR). CKD is associated with increased cardiovascular risk (predominantly stroke, ischaemic heart disease and heart failure) (3–7), and increased all-cause mortality (4–6), however disease progression can be delayed if it is identified early (1,8). The majority of patients (98%) are managed in primary care using a multifactorial approach of: repeated monitoring; maintenance of blood pressure below agreed guideline limits (140/90mmHg, or below 130/80mmHg in those with diabetes or raised proteinuria); treatment of hypertension with angiotensin-converting-enzyme inhibitors (ACE inhibitors) or Angiotensin II Receptor Blockers (ARBs); and encouragement to lead a healthy lifestyle (1).

Monitoring forms a major part in managing long term illness. It is an important element of health care; however, despite the substantial costs it entails, it has been neglected as an area for research. Guideline bodies often find there is a lack of evidence on which to make recommendations, for example regarding the frequency of monitoring (9). Although good monitoring can improve patient outcomes, poor monitoring may be an expensive waste of resources, not only incurring huge cost to the National Health Service (NHS) but also leading to inappropriate treatment and patient inconvenience as well as absence from work.

There has been a dramatic increase in the use of laboratory testing over recent decades, particularly repeat testing or monitoring. CKD management guidance from the National Institute for health and Care Excellence (NICE) (2) recommends that the frequency of serum creatinine monitoring should depend on the clinical situation, with more frequent monitoring in patients with poorer kidney function; figure 1 shows the recommended frequencies by category of eGFR and Albumin Creatinine Ratio (ACR).

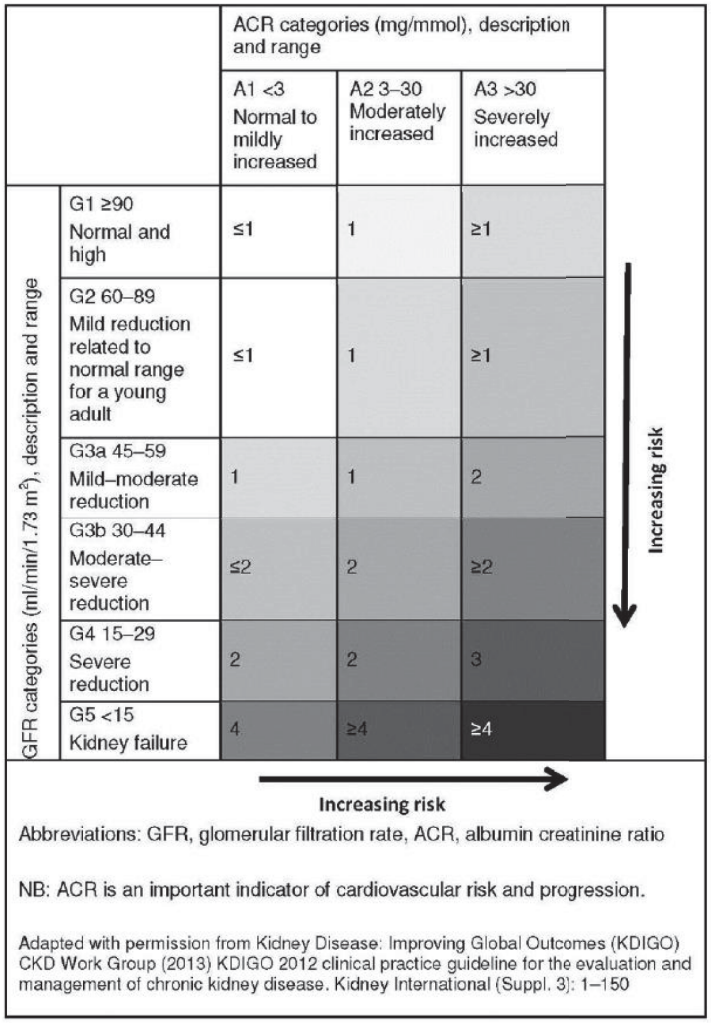

Figure 1: Frequency of monitoring of GFR (number of times per year, by GFR and ACR category) for people with, or at risk of, CKD. From the National Institute for health and Care Excellence Clinical Guideline 182: Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care (2)

NICE management guidelines also recommend that testing should be offered to people with a number of comorbidities such as diabetes, hypertension and cardiovascular diseases, but that age, gender and ethnicity should not be used for distinguishing whether or not a person should be tested (1). A recent study in south-west London found that testing was carried out unequally across different age, gender and ethnic groups (10), however variation in the rate of kidney function testing and potential differentials between different populations groups have not previously been characterised at the national level. The use of data from the CPRD would provide a comprehensive picture of current monitoring practice, allow us to estimate the proportion of tests that are for monitoring as opposed to diagnostic purposes, and

provide insight into evolving trends and potential differentials in testing. Kidney function testing is also recommended in subjects treated with certain medications, such as antihypertensive agents and non-steroidal anti-inflammatory drugs (NSAIDs) (2). Previous research within the General Practice Research Database (GPRD, now CPRD), has examined rates of creatinine testing (and other biochemical testing) in subjects beginning antihypertensive drug treatment (11,12). Our analyses will extend this previous work to examine testing rates in a wider population and for other prescriptions where creatinine and/or proteinuria testing is recommended.

Furthermore, while these guidelines do provide recommendations for the frequency of monitoring, the recommendation is largely based on the consensus opinion of the Guideline Development Group using indirect evidence on progression of CKD from a literature review; no economic analyses were found (2). Similar monitoring frequencies, based on consensus of the Guideline Development Group, were also recommended in earlier NICE guidelines (1), which also specifically recommended that further research is "undertaken to identify more accurate and cost effective methods of monitoring kidney function, especially in patients with [glomerular filtration rate] (GFR) 60 ml/min/1.73m2 or more" (1). We propose to address this evidence gap using previously described methods for the analysis of monitoring regimes (13–16).

Objective and specific aims

The overall objective of this study is to describe and improve kidney function testing in UK primary care. The tests of interest will be serum creatinine blood tests to determine a patient's estimated Glomerular Filtration Rate (eGFR), and proteinuria urine tests.

Aim 1: To describe rates of kidney function testing since the introduction of the Quality Outcomes Framework (QOF) for general practice.

The number of serum creatinine and proteinuria tests requested in each calendar year from 2005 to 2013 (9 years inclusive) will be examined by region (strategic health authority (SHA)), presence/absence of major patient comorbidities (diabetes, hypertension, cardiovascular disease, atrial fibrillation etc.) and subdivided into monitoring and diagnostic tests.

Aim 2: To identify the most effective monitoring strategy for different stages of CKD.

Current guidelines from NICE suggest a range of monitoring intervals by stage of CKD and category of ACR, however these recommendations are largely based on consensus opinion of the Guideline Development Group (GDG) (2). We will use a modelling approach to find evidence-based recommendations for intervals of monitoring different stages of CKD.

Study Type

Descriptive study (aim 1) and hypothesis generating (aim 2).

Study design

Open cohort study.

Sample size

A recent study of GP records from practices in south-west London found that 28% of men and 24% of women (aged 18 to 75+ years) had a serum creatinine test recorded in their general practice record (10). Assuming therefore that about one quarter of adults in the CPRD will have at least one serum creatinine test, we expect to have more than adequate data for our research questions regarding serum creatinine. Proteinuria testing is rare (~1%; reference (10)). To estimate a proportion of about 1%, with 95% confidence and precision +/-0.1%, requires 27,500 patients; therefore even our analyses of proteinuria should in general have sufficient data. However if any subgroup has fewer subjects than this, we will handle this through reporting of confidence intervals (as for all analyses) and cautious interpretation.

For aim 2, analysis will use repeated measurements of eGFR (calculated using recorded serum creatinine levels). Planned analysis methods do not require large numbers (17); our previous successful project on HbA1c monitoring in people with type 2 diabetes used data from a cohort of 200 subjects (16).

Data Linkage (if applicable)

ONS mortality linkage is requested. Cause of death data will be used to inform the individual simulation models we will fit for Aim 2. Linkage to integrated Hospital Episode Statistic (HES) data is also requested. Kidney dialysis, transplantation and end-stage renal disease are other important end points in our health economic modelling; while read codes are available within CPRD, we believe the addition of secondary care International Classification of Diseases (ICD) codes from integrated HES will improve the accuracy of ascertaining dates of these events.

Linkage to the Index of Multiple Deprivation is also requested. Recent evidence suggests that socioeconomic inequalities in the care for chronic conditions such as CKD have persisted, even after the introduction of pay for performance systems like the Quality Outcomes Framework (18). Describing potential differentials in current practice by level of deprivation is therefore an important part of analyses in aim 1, and deprivation may be a relevant covariate for analyses in aim 2.

Study population

This is an open cohort study of adult patients (≥ 18 years of age) registered at "up-to-standard" CPRD practices (both with and without linkage) and who are deemed to have "acceptable" patient records, excluding patients who were pregnant in the 12 months preceding study entry and patients who have had renal transplantation at any time prior to study entry. Analyses for aim 1 will include subjects from practices with and without linkage, other than analyses examining deprivation which will be restricted to linked practices. Analyses for aim 2 will all be restricted to practices with linkage available.

Follow-up

The study start date will be 1st January 2005 (this date is after the publication of the KDOQI guidelines (19) for classification of CKD in 2002, and after the introduction of QOF targets in UK primary care in 2004).

Eligible patients will be registered with the practice for a minimum of 12 months prior to study entry (to ensure adequate recording of baseline covariates). Eligibility will be defined using all available data prior to entry date.

Study end date will be 31st December 2013 (or date of last available linked data). Follow-up ends at this date or (if earlier) at time of death or transfer out of CPRD or (where applicable) date of becoming pregnant or undergoing renal transplantation or dialysis (when no read code diagnosis of acute kidney injury is also present).

Hence the study index date for each patient will be the latest of the following dates: study start date, practice up-to-standard date, date of 18th birthday and date of registration with the practice plus 12 months. Patient records will be censored at the earliest of the following dates: study end date, date of last upload of practice data, date of death, transfer out date, date of incident record of pregnancy within study period and date of incident record of renal transplantation or dialysis within study period.

Selection of comparison group(s) or controls

No comparison or control groups required .

Exposures, Outcomes, and Covariates

Aim 1: To describe rates of kidney function testing.

Outcomes:

- Number of serum creatinine tests
  The number of tests will be extracted using entity codes for serum creatinine (code 165) and read codes indicating serum creatinine testing (see Appendix for code list). A maximum of one test per date will be counted.
- Number of proteinuria urine tests
  The number of tests will be extracted using entity codes for urinalysis protein (287) and urine microalbumin (code 435). We will also use read codes indicating proteinuria testing (see Appendix for code list). A maximum of one test per date will be counted.
- Kidney function tests
  Read codes for kidney function tests that cannot be identified as creatinine or proteinuria tests using entity codes will also be counted separately (see appendix for read codes). A maximum of one test per date will be counted.

Exposures:

- Diagnosis of CKD. Stage of CKD will be defined using relevant diagnostic codes specifically indicating CKD with or without stage information (see Appendix for list of read codes).
  - In sensitivity analyses, we will additionally use eGFR values to define CKD stage (two consecutive eGFR values separated by 90 days or more within the relevant ranges(1)). This combination of diagnostic codes and eGFR values has been used to define CKD by stage in previous research using primary care data (20,21). GFR will be estimated using the Modification of Diet in Renal Disease (MDRD) equation (22), as recommended by the national guidelines over the study period (1).
  - Because eGFR readings over 60 ml/min/1.73m^2 are less accurate than lower readings, we will group stages 1 and 2 together into a "mildly impaired eGFR" group.
- Year of test

- Region (SHA)
- Age at test
- Major comorbidities including diabetes, hypertension, ischaemic heart disease, chronic heart failure, peripheral vascular disease, transient ischaemic attack and stroke, thyroid disease, atrial fibrillation, non-melanoma skin cancer and prescription of non-steroidal anti-inflammatory drugs (NSAID) (categories for length of use: no use, <1 year, 1-3 years, 3-5 years, ≥5years)
- Reason for testing (monitoring, diagnostic work-up, and drug toxicity monitoring) see Analysis section of this protocol for further detail).
- Gender
- Ethnicity
- Deprivation

We will define comorbidities using the recording of a relevant diagnostic code (read code) and/or a treatment codes as appropriate. These methods will be based on QOF coding and our previous experience using data from the GPRD/CPRD (protocol numbers 10_038, 10_071, 12_091R). For example, for each time point, history of cardiovascular disease, e.g. chronic heart failure, will be defined using the recording of at least one relevant read code prior to the time point of interest, whereas diabetes status at each time point will be defined using the recording of a relevant diagnostic code (read code) and/or a treatment code for diabetes prior to the time point of interest, and will exclude patients with secondary diabetes, for example gestational or corticosteroid-induced diabetes.

*Aim 2:*To identify the most effective monitoring strategy for different stages of CKD.

Analyses will be restricted to patients with a diagnosis of CKD, defined using relevant diagnostic codes (see Appendix).

Outcome:

- eGFR at study entry and at the time of each test

- Serum creatinine values will be obtained using entity code 165, and when associated with a relevant read code (see appendix for serum creatinine code list), general serum testing entity code.
- For our primary analysis we will use the CKD-EPI equation to calculate eGFR based on recorded values of serum creatinine, gender, age at test and ethnicity (23); this equation is recommended in current NICE guidelines (2)
- In sensitivity analyses we will compare to other estimates of eGFR: in particular, the MDRD equation (recommended by NICE over the period data were collected).

Exposures:

- Age at each test will be used as the unit of time.
- Gender
- Year of test
- Stage of CKD

NICE guidance recommends different monitoring intervals for patients with different stages of CKD, we will report results stratified by stage of CKD, grouped as CKD stages 1 and 2, stage 3a, stage 3b. Additionally, during model estimation, we will test whether model fit is improved by adjustment for or stratification by level of proteinuria (see Figure 1, NICE guidance).

Previous research has indicated that CKD screening is likely to be cost-effective in people at increased risk of kidney disease, such as those with hypertension or diabetes (24). Sensitivity analyses will examine whether blood pressure treatments and comorbidities (diabetes, hypertension), modify CKD progression. Health economic modelling will extend progression to stages 4 and 5, and will also use additional covariates (ethnicity, blood pressure (systolic and/or diastolic, last record in preceding two years), deprivation, smoking status (last record in preceding two years), BMI (last record in preceding two years), diabetes, cardiovascular disease, lipid profile (total cholesterol and HDL cholesterol, last record in preceding two

years)), subgroup size permitting, to evaluate effects driven by different monitoring regimens and treatments in the management of disease.

Analysis

Data management and analyses will be carried out using Stata 12.1 and R. (25,26).

Aim 1: To describe rates of kidney function testing.

Details of the number and clinical results (values) of serum creatinine and proteinuria tests requested by GPs during the study period for each patient will be analysed. Further demographic and comorbidity data on each patient will also be used for some analyses.

We will summarise rates of serum creatinine and proteinuria testing separately in tables.

The following will be reported for all patients and by diagnosed stage of CKD:

a) The number of patients with at least one record of testing (and additionally the number of patients with repeat tests; e.g. 2, 3, 4 or more tests).
b) Of those, the number with repeated tests versus those with isolated tests (e.g. first test in >2 years, not followed by another test in <2 years)
c) Tests will be subdivided into those concurrent with a prescription of drugs in which kidney function testing is recommended for monitoring purposes or prior to prescription.

The above categories are chosen to give an indication of the burden of testing attributable to CKD monitoring, diagnostic work-up, and drug toxicity monitoring. The denominator will include all adult patients (≥ 18 years of age) registered at "up-to-standard" CPRD practices (both with and without linkage) and who are deemed to have "acceptable" patient records, excluding patients who were pregnant in the 12 months preceding study entry and patients who have had renal transplantation at any time prior to study entry.

We will also examine numbers by age groups; by the presence/absence of major patient comorbidities (diabetes, hypertension etc.); and by NHS region.

Where appropriate, we will use statistical tests (e.g. Chi-squared tests) to formally test associations between patient characteristics, year or region on testing rates. To examine associations between covariates and testing for kidney function simultaneously across all time periods, we will use multi-level mixed effects logistic regression; analyses examining deprivation as a covariate will be restricted to patients registered at practices with linkage to IMD.

*Aim 2:*To identify the most effective monitoring strategy for different stages of CKD.

These analyses will use repeated measures of eGFR, appropriate diagnostic and referral codes for renal impairment or end-stage renal failure, and ONS data for date of death. We will build statistical models for the progression of CKD that account for the uncertainty or short-term variation in eGFR. Methods for estimating these parameters have been described in detail elsewhere (13,16); briefly we favour a random-effects modelling approach. We propose to treat eGFR as a continuous variable. However, model assumptions will be checked, and if substantially violated, we will instead model CKD stage as a categorical variable, using statistical models previously developed for diabetic nephropathy and diabetic conditions (27). We will evaluate the impact of different monitoring intervals for different levels of risk factors. Risk factors will include baseline eGFR or CKD stage, hypertension, proteinuria, age and history of cardiovascular events.

The main analysis will use standard deviations to quantify variability; in a methodological add-on we will compare this to the use of co-efficient of variation, variation independent of mean and standard deviation independent of the mean (28) for quantifying variability.

Individual patient simulation models, informed by the analysis on progression of CKD, will then be used to evaluate monitoring strategies that differ by timing and frequency of monitoring and management strategies. Current monitoring strategies will be compared with alternative strategies (e.g. biannual, annual and biennial monitoring, or other intervals as indicated by results) to identify the most effective and cost-effective scheme. For each monitoring strategy, we will estimate the incidence of true disease and probability of stage misclassification.

Parameter estimates from these models and data on risk factors listed above (along with estimates from ongoing systematic reviews and unit cost data, such as the cost of appointments and of procedures, from external sources (e.g. Unit Costs of Health and Social Care 2013 (29)) will contribute to the development of a cost-effectiveness model of monitoring patients with CKD in the UK population. For the purpose of evaluating costs, CPRD data will be used to establish the characteristics of people diagnosed with CKD and estimate numbers of appointments for the purpose of diagnosis and monitoring of kidney disease and other relevant primary care costs related to CKD stage. External data will be used for hospital and other healthcare costs of people diagnosed with CKD in UK (e.g. (30)). We have previously used these methods to provide transition probabilities for an economic model in an Health Technology Assessment funded project on monitoring diabetic nephropathy (31). Current guidelines for economic modelling will be followed in reporting and presenting the results of this analysis (32). The model will estimate the cost per quality-adjusted life year (QALY) of various screening and monitoring policies to help identify the optimal levels of screening, monitoring and management strategies in different patient groups a UK context.

Validation of the models:

We will use a number of approaches to assess the internal validity of the model, and validity of the results, as follows: internal validation will consist of checking that assumptions of the

model are met and that the model recreates the observed distributions of the stages of CKD, end stage renal disease and mortality over the time frame of the data (apparent validation). We will compare the model based estimates of intra-individual variation (biological and assay) in eGFR with estimates from the literature. Finally, we will use bootstrap resampling to produce estimates of uncertainty in the main model outputs (proportions of false positives and false negative tests).

Missing data

For the assessment of clinical diagnosis/ disease in individuals, we will assume that absence of any relevant medical read code in the clinical record means true absence of disease. For other covariate measures that may not be accurately/ regularly recorded at yearly intervals, we will use multiple imputation methods if the necessary assumptions are met (33).

The random-effects models, to be fitted as part of aim 2, fit time (age) as a continuous measure, and therefore allow for irregular repeat measures.

Patient or user group involvement

As part of the grant proposal, this project has been reviewed by individuals with long term conditions that require frequent monitoring, as well as nurse practitioners and GP commissioners. Patient and Public Involvement (PPI) members have also been invited to the Steering and Senior Management groups. A PPI expert is also involved as a strategic consultant in this programme of work.

Limitations of the study design, data sources, and analytic methods

In Aim 2 we are using a modelling approach rather than a randomised controlled trial of different approaches to monitoring kidney function, but we consider this a cost-effective way

to examine different monitoring schemes using statistical methods that have previously proven useful. Additionally, due to a limited time horizon of clinical trials, life-time results would still need to be based on a model.

An unavoidable limitation is that CRPD analyses often require the use of measurements taken at different times (e.g. blood pressure at one visit, weight at another) rather than concurrently, hence the decision to use multiple imputation methods for data that is missing during the relevant time periods.

The proposal as a whole is also subject to the usual caveats for statistical modelling based on observational data, and to the usual limitations of routinely collected data for research.

Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The results from both project aims will be submitted for presentation at academic conferences and for publication in scientific journals. It is expected that Aims 1 and 2 will each form at least one publication, with both being prepared by Summer 2016; the results of cost-effectiveness analyses require input from the rest of the programme of work so will be finalised in 2017/2018.

Amendments

The following amendments are proposed.

Exposures, Outcomes and Covariates

This amendment affects analysis of Aim 2 only.

For Aim 2 only, we propose to define the inclusion criterion CKD, and exposure variable stage of CKD, from biochemical measurements (eGFR) instead of diagnostic codes. This is because our GP colleagues advise that not all patients with impaired eGFR may have been assigned CKD diagnostic codes. Aim 2 is to identify appropriate monitoring strategies for different stages of CKD by studying rate of change of eGFR in each stage of CKD. For this we wish to classify CKD, and its stages, as accurately as possible.

The methods for calculating eGFR from serum creatinine are already documented in the protocol.

(Note that for Aim 1 we will continue to assign the exposure variable CKD by recorded diagnostic codes rather than biochemical measurements. This is because the exposure in aim 1 is explicitly *diagnosis* of CKD: to describe the monitoring of CKD in those known to their GP to have CKD.)

Follow-up

For the cost-effectiveness analysis in Aim 2, a study start date of 1st July 2004 will be used (replacing the study start date of 1st January 2005), to ensure ten years of follow-up and hence give comparability of our results with the ten-year risk equations used in UK guidelines for prevention of CVD.

Plans for disseminating and communicating study results …

This amendment affects publication plans only. No additional analyses will be carried out, but we propose to publish separately an intermediate analysis that contributes to the cost-effectiveness modelling that is described in the Analysis section under subheading Aim 2.

The original protocol anticipated publication of the cost-effectiveness model as a single publication: components of the model would appear as a Table or a part of a Table or an Appendix.

In the light of current interest in CKD as a risk factor for cardiovascular disease, we now consider the component of the model quantifying risk of first CVD among CKD patients without previous cardiovascular disease to be of interest in its own right. We therefore additionally propose (a) a conference abstract (b) a student dissertation at MSc level and (c) potentially, a manuscript based on these, describing this component of the CVD submodel and its interpretation. Any such publication(s) would reflect the status of this as a part of a larger cost-effectiveness model of monitoring CKD rather than a stand-alone research project.

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Code lists

Code list for Chronic Kidney Disease

medcode	readcode	readterm	databasebuild
104981	K05..13	Chronic kidney disease	Sep-12
29013	1Z10.00	Chronic kidney disease stage 1	Feb-09
105392	K051.00	Chronic kidney disease stage 1	Dec-12
94789	1Z17.00	Chronic kidney disease stage 1 with proteinuria	Feb-09
95572	1Z18.00	Chronic kidney disease stage 1 without proteinuria	Feb-09
12586	1Z11.00	Chronic kidney disease stage 2	Feb-09
105383	K052.00	Chronic kidney disease stage 2	Dec-12
95146	1Z19.00	Chronic kidney disease stage 2 with proteinuria	Feb-09
95121	1Z1A.00	Chronic kidney disease stage 2 without proteinuria	Feb-09
12566	1Z12.00	Chronic kidney disease stage 3	Feb-09
104619	K053.00	Chronic kidney disease stage 3	Jul-12
94793	1Z1B.00	Chronic kidney disease stage 3 with proteinuria	Feb-09
95123	1Z1C.00	Chronic kidney disease stage 3 without proteinuria	Feb-09
94965	1Z15.00	Chronic kidney disease stage 3A	Feb-09
95408	1Z1D.00	Chronic kidney disease stage 3A with proteinuria	Feb-09
95175	1Z1E.00	Chronic kidney disease stage 3A without proteinuria	Feb-09

95179	1Z16.00	Chronic kidney disease stage 3B	Feb-09
95178	1Z1F.00	Chronic kidney disease stage 3B with proteinuria	Feb-09
95177	1Z1G.00	Chronic kidney disease stage 3B without proteinuria	Feb-09
12479	1Z13.00	Chronic kidney disease stage 4	Feb-09
104963	K054.00	Chronic kidney disease stage 4	Sep-12
95122	1Z1H.00	Chronic kidney disease stage 4 with proteinuria	Feb-09
95406	1Z1J.00	Chronic kidney disease stage 4 without proteinuria	Feb-09
12585	1Z14.00	Chronic kidney disease stage 5	Feb-09
105151	K055.00	Chronic kidney disease stage 5	Nov-12
95508	1Z1K.00	Chronic kidney disease stage 5 with proteinuria	Feb-09
95405	1Z1L.00	Chronic kidney disease stage 5 without proteinuria	Feb-09
97980	1Z17.11	CKD stage 1 with proteinuria	Nov-09
97979	1Z19.11	CKD stage 2 with proteinuria	Nov-09
97978	1Z1A.11	CKD stage 2 without proteinuria	Nov-09
95145	1Z1B.11	CKD stage 3 with proteinuria	Feb-09
95188	1Z1C.11	CKD stage 3 without proteinuria	Feb-09
95571	1Z1D.11	CKD stage 3A with proteinuria	Feb-09
95176	1Z1E.11	CKD stage 3A without proteinuria	Feb-09
95180	1Z1F.11	CKD stage 3B with proteinuria	Feb-09
100633	1Z1G.11	CKD stage 3B without proteinuria	Sep-10

99312	1Z1H.11	CKD stage 4 with proteinuria	May-10
97587	1Z1J.11	CKD stage 4 without proteinuria	Sep-09
99160	1Z1K.11	CKD stage 5 with proteinuria	Apr-10
97683	1Z1L.11	CKD stage 5 without proteinuria	Sep-09

Code list to indicate serum creatinine testing

medcode	readcode	read term
5	44J3.00	Serum creatinine
3927	44J3300	Serum creatinine raised
31277	44J3000	Serum creatinine abnormal
26903	44J3200	Serum creatinine normal
35545	44J3100	Serum creatinine low
42345	44J3z00	Serum creatinine NOS
45096	44JD.00	Corrected serum creatinine level
13736	44JF.00	Plasma creatinine level
62062	44JC.00	Corrected plasma creatinine level
27095	4Q40.00	Creatinine level
39905	4I37.11	Creatinine in sample
13736	44JF.00	Plasma creatinine level

Additional codes to indicate serum creatinine testing in aim 1.

medcode	readcode	read term
23250	451E.00	GFR calculated abbreviated MDRD

30898	451G.00	GFR calculated abbreviated MDRD adj for African Americ orign
19747	451F.00	Glomerular filtration rate
90871	7P14000	Glomerular filtration rate testing

Code list to indicate proteinuria testing

medcode	readcode	read term
1802	4678.00	Proteinuria
38284	R110z00	[D]Proteinuria NOS
11248	R110.00	[D]Proteinuria
13613	46N2.00	urine protein abnormal
14395	46N..00	urine protein
14429	46N3.00	urine total protein
27059	467Z.00	urine protein test NOS
27214	46NZ.00	urine protein NOS
43262	467H.00	random urine protein level
27266	44lD.00	Urine protein/creatinine ratio
44179	46N7.00	urine protein/creatinine index
5451	R110000	[D]Albuminuria
10924	R110300	[D]Microalbuminuria

14410	46N4.00	urine albumin
14563	46W..00	Urine microalbumin
17106	46W1.00	Urine microalbumin negative
28180	46W0.00	Urine microalbumin positive
31969	4I3B.11	Albumin in sample
39248	46N8.00	urine microalbumin profile
2607	46TC.00	Urine albumin:creatinine ratio
14113	44J7.00	Albumin / creatinine ratio
14391	46TD.00	Urine microalbumin:creatinine ratio

Kidney function testing

medcode	readcode	readterm
8662	8A6..11	kidney function monitoring
11995	451..11	kidney function tests
22327	R144.11	kidney function test abnormal
5458	8A6..00	Renal function monitoring
2998	451..00	Renal function tests
10768	R144.00	[D]Renal function test abnormal
3980	4512.00	Renal function tests abnormal

4265	4511.00	Renal function tests normal
26001	4519.00	Deteriorating renal function
13812	44J..00	Blood urea/renal function
25763	4516.00	Renal function tests borderline
26943	44JZ.00	Blood urea/renal function NOS
37236	451Z.00	Renal function test NOS
56293	4515.00	Differential renal function
101976	451H.00	Recovery of renal function

Appendix 5 Systematic review and meta-analysis comparing the bias and accuracy of the Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration Equations in community-based populations

McFadden *et al.*[24] https://doi.org/10.1373/clinchem.2017.276683

Appendix 6 Effects of antihypertensives, lipid-modifying drugs, glycaemic control drugs and sodium bicarbonate on the progression of stages G3 and G4 chronic kidney disease in adults: a systematic review and meta-analysis

Taylor *et al.*[25] https://doi.org/10.1136/bmjopen-2019-030596

Appendix 7 Statistical models for the deterioration of kidney function in a primary care population: a retrospective database analysis

Oke *et al.*[26] https://doi.org/10.12688/f1000research.20229.1

Appendix 8 An observational cohort study of primary care patients with reduced estimated glomerular filtration rate

Flemming *et al.*[86] https://doi.org/10.3399/BJGP.2020.0940

Appendix 9 Qualitative evaluation of monitoring chronic kidney disease and chronic heart failure with patients and health practitioners

Overview

Aim

These WSs aimed to use qualitative methods to explore patients' and health professionals' experiences of, and views about, monitoring for CKD and CHF. This was achieved through analysis of individual patient interviews and focus group interviews with GPs, practice nurses and CHFNs. Qualitative research methods are widely regarded as the most appropriate means of collecting, analysing and understanding patients' experiences.

Alterations to the original study design

The original design for the patient interview studies had been to use the same methodology for both conditions. This comprised a secondary analysis of existing data sets from the Nuffield Department of Primary Care Health Sciences (NDPCHS) Health Experiences Research Group's (HERG's) archive of studies published on the health information website https://healthtalk.org/ (accessed 5 May 2020), followed by new interviews to explore, in more depth, issues raised by the secondary analyses. However, owing to unforeseen delays, a collaborative research project between the University of Bristol, University of Manchester, University College London, University of Southampton and University of Oxford to produce the CKD data set had not been started, so a different approach was taken for the CKD patient study.

The work to produce the CKD patient interview collection took place in collaboration with the current work programme, with additional funds from the National Institute for Health Research School for Primary Care Research (project reference number NSPCR ID FR4.120). This enabled the incorporation of questions about patients' experiences of being monitored in the primary study. One-third of the interviews were conducted by the Oxford-based researcher from the current work programme (JE), the remainder by a researcher in Bristol. The researchers collaborated closely, using the same methodology and interview guide, and jointly analysed the data. All interviews were conducted using existing HERG ethics approval and were copyrighted to the University of Oxford, with permission for sharing with other researchers.

For the focus group study, rather than convening separate groups to discuss CKD and CHF, we decided to discuss both conditions in each group except for those involving just CHFNs. Focus groups were conducted with each professional group separately.

Methodology used for all patient interviews

The methodology used for all HERG studies leading to publication on https://healthtalk.org/ (accessed 5 May 2020) has been tried and tested since 2000 (see https://healthtalk.org/uploads/files/HERGresearch.pdf); accessed 25 January 2021, approved by the NHS National Research Ethics Service Committee South Central – Berkshire (reference number 12/SC/0495) and recommended by the NHS National Knowledge Service as the 'gold standard' for research into patient experiences. All patient interviews included in the current work programme were collected and analysed using the HERG methodology and ethics approval.

For all HERG/healthtalk studies, 40–50 interviewees were sought from a range of backgrounds, age groups, geographical areas and experiences of health care, with the aim of achieving a 'maximum variation sample'.[87] Interviews took place in a person's home or another place of their choice. Participants were asked to tell the story of their illness or health condition, without interruption from the researcher, after which questions were asked to elicit more detail or raise issues not mentioned by the participant. Interviews typically lasted between 40 and 120 minutes. Interviewing continued until data saturation was reached on key categories, such as experiences of diagnosis and treatments, and information and support needs, and no new themes emerged. Interviews were recorded and transcribed verbatim and returned to the participant for optional review. Transcripts were anonymised and coded using qualitative data indexing software (NVivo; QSR International, Warrington, UK). The data in each coding report were then thematically analysed in detail. Analyses were written with the aim of explaining 'what is going on in the data' while taking account of all the issues raised, not just the most common ones.

The chronic heart failure patient study

Method

The existing CHF collection consisted of 43 patient interviews conducted between 2003 and 2013. For the current work programme, 16 new patient interviews in 2015 focused on monitoring, which had received little attention in the original collection. Interview guides for the original and new interviews are presented in *Tables 1* and *2*. *Table 3* presents sample characteristics. The secondary analysis of the existing interview collection was conducted first so that the findings could inform the new interviews. Using Heaton's categories of secondary analysis,[88] our approach was that of 'supra-analysis' (examining new empirical, theoretical or methodological questions that were not the focus of the primary study). The analysis aimed to focus on patients' attitudes to both the content and frequency of monitoring, adherence to and understanding of medications, and triggers to consultation.

TABLE 1 The CHF failure interview guide – existing collection (43 patient interviews conducted between 2003 and 2013)

Questions	Prompts
Could you tell me how you first discovered that you had heart failure? How did it start? What made you seek help/ medical advice?	• What were the symptoms to begin with? • Can you describe what made you realise you had become ill? (e.g. breathlessness, extreme tiredness, feeling unable to cope with everyday things like work/your usual social activities) • What made you seek advice? • What happened next?
When you were diagnosed with heart failure, what were you told about the illness? Who told you that you had heart failure and how did s/he go about it? How did you feel about it at that time? What were you told about heart failure?	• Would you have liked more/less information? • How has your understanding of heart failure and what it means to live with it changed since your initial diagnosis? • Who did you go to and what happened to you (e.g. were you in hospital, which one, for how long, what tests did you have)?
What do you think caused you to have heart failure?	None
What did you know about heart failure before you found out that you had it?	Do you know anyone else who has heart failure?
What do you understand heart failure to mean?	None
Have you wanted to find out more about heart failure since your first diagnosis?	• Has anyone other than your doctor helped you find out anything about heart failure? How did they do so? • Have you actively tried to find out more about it? If so how … books? Internet? Leaflets in surgery or hospital? • Family and friends passing information on to you? • Would you recommend anything in particular you have read or seen about heart failure to others?

TABLE 1 The CHF failure interview guide – existing collection (43 patient interviews conducted between 2003 and 2013) (*continued*)

Questions	Prompts
Have you had any other medical problems and can you tell me about them?	How have they affected your heart failure? And medication for them?
(Given that you may have had lots of treatment for heart failure) Can you tell me now about the treatment you have had so far?	• Hospital admissions, for instance? What took you to hospital? How many operations and what were they for? How long was your stay? (e.g. pacemaker to help heart keep regular rhythm, left ventricular volume reduction, replacement heart valve because of heart disease, LVAD to help failing heart while patient awaiting heart transplant) • How long did it take you to recover from the operation? • Tests? (e.g. echocardiography/ultrasonography, ECG, chest X-ray) – what happens when you have an echocardiogram . . .
Are you having any home visits from nurses now and what do they do?	None
Other people will be interested in the kind of medicine you're taking, so can you tell me which drugs you're taking at the moment and what they do to you?	None
What do they make you feel like? (e.g. diuretics can cause leg cramps, need to go to loo often and urgently.) Are you aware of any side effects now or in the past?	• How do you remember to take these pills? (e.g. specially labelled box, special place for pills, taken at mealtimes) • What do you do if you forget to take a pill? • Have you ever chosen not to take any of your medicines for any reason? Have you talked about this with your doctor at all/have you ever felt like asking for your medicines to be reviewed?
(You mentioned breathlessness/tiredness/not coping) . . . can you describe what it feels like when you have an episode of this?	How do you usually cope with your breathlessness/tiredness/not coping?
How has heart failure affected you physically?	• Can you still do the same kinds of things that you did before? (e.g. driving a car, walking to the shops, cooking a family meal, carrying bags of shopping/piles of clean clothes upstairs) • Any other side effects (e.g. lethargy, confusion) and how do they affect your daily routines?
What about your usual way of life; can you describe how heart failure has affected that?	• Have you had to stop walking, sport, drinking or smoking? What kind of holidays do you have? • How have you found these changes?
What kind of effect has heart failure had on you and your family?	• How did you feel? Did it affect the way you feel about yourself? Did it affect other people? • Who did you tell and how did they react?
What about the mental and emotional side of living with heart failure? How have you found that?	• Can you describe how you are getting on with your life now that you have heart failure? • Has it affected your moods or your outlook on life? • What about your wife/husband, how does she/he find you now that you have heart failure? • In what ways, if at all, have your relationships with wife/children/close friends/colleagues been affected? • What sort of support have they given you?
What are your thoughts about the future and do you talk to anyone about your thoughts?	• Have you talked to anyone (your wife/children/close friend/doctor/nurse about the future?) • Would it be helpful to share your thoughts about heart failure with anyone else?

continued

TABLE 1 The CHF failure interview guide – existing collection (43 patient interviews conducted between 2003 and 2013) (*continued*)

Questions	Prompts
Are there any messages that you would like to give to doctors and nurses about the treatment of heart failure? Are there still questions about heart failure that you would like answered?	None
What kinds of advice, based on your own experience of living with heart failure, would you like to pass onto others with the same condition?	Living with it, partnerships, changing your lifestyle
Is there anything else I've not mentioned about living and coping with heart failure that you would like to tell me?	

ECG, electrocardiography; LVAD, left ventricular assist device.

TABLE 2 The CHF interview guide (16 new patient interviews conducted in 2015)

Topic	Questions
Part 1: initial open-ended question to elicit narrative	
As you know, my study is focusing on how people's heart failure is monitored or managed, but, in order to get some background about your situation, please could you spend a few minutes telling me about the following three things: 1. How you found out you'd got heart failure 2. How it affects you 3. How it is managed day to day I will ask you to start talking about each of those three things separately, and, when you have done that, I will ask you some more detailed questions	
Part 2: ask any specific questions to seek clarification about anything in part 1	
Then cover the following topics as required to elicit further information (time allowing) in any order, but with an emphasis on monitoring	
Understanding heart failure	• Who told you that you have heart failure? • Has your understanding of your heart condition changed over time? (Note: heart failure with left ventricular systolic dysfunction = not pumping out; heart failure with preserved ejection fraction = not filling) • What do you think caused your heart problem/failure? (Note: possible causes include heart attack, hypertension, heart muscle disease, birth defects, irregular heart beat, damaged heart valves, damaged heart muscle from viral infection or long-term heavy drinking, some cancer treatments) • Or what events led up to it? (e.g. other heart conditions, diagnostic tests – echocardiography, bloods, BNP, urine, breathing, ECG) • How long have you known about this problem with your heart? • What does it mean to you to have it?
Other health conditions	Do you have any other health problems/medical conditions? • If so, how does it/do they interact or interfere with your heart condition? • Which condition affects you most? • Which condition causes you the most concern?

Heart treatments past and present	• What treatments have you had for your heart up to now? (Note: may include angioplasty, surgery, valve replacements, resynchronisation devices, transplant, medication)
	• Have you ever been admitted to hospital because of your heart condition?
	  ○ If so, please tell me what caused this
	  ○ What happened in hospital?
	  ○ And after you were discharged from hospital? (Note: including getting medication back on track)

TABLE 2 The CHF interview guide (16 new patient interviews conducted in 2015) (*continued*)

Topic	Questions

	• Please can you tell me about your current medication – what are you taking and when, what are they for, and what effects do they have on you?
	• Have you ever experienced any troublesome side effects from any of your medicines?
	  ○ What effect and from which drug (if known)?
	  ○ Were any changes made to your prescribed medicines as a result?
	  ○ What changes and with what effect?
	• How do you feel about having to take these prescribed medicines?
	• Do you always take them as prescribed?
	  ○ If no, why not? (Note: through choice, forgetting, or approved self-management of diuretics)
	• How do you remember to take them?
	• Do you take any over-the-counter or complementary medicines?
	  ○ If yes, what medicines and for what problem?

Monitoring	• How often do you have contact with a health professional about your heart health? (Note: should be at least every 6 months for stable patients, more frequent if clinical condition or medication has changed)
	• Who do you see? (specialist, GP, CHFN, practice nurse, other)
	• Where do these checks take place? (hospital, practice, community heart failure clinic, their home)
	• What checks are done on you? [Note: should include clinical assessment of functional capacity, fluid status, cardiac rhythm (pulse), cognitive status, nutritional status, medicines review, bloods – serum urea, electrolytes, creatinine, eGFR]
	• Do you know what each test is for?
	• How do you find out the results of tests? (e.g. blood tests)
	• How much detail are you given about test results?
	• Do you understand what you are told about test results?
	• How do you feel about the level of information you are given about your test results?
	• Do you monitor any aspects of your heart health yourself at home?
	  ○ If yes, what and how often? [Note: may include symptoms, weight (how often?), ECG]
	  ○ Please tell me about any special equipment you have for this. (e.g. ECG kit, blood pressure monitor, weighing scales, remote monitoring for implanted devices)
	  ○ How do you record these measurements and pass them to the health professionals who are looking after you? (paper, electronically or by telephone)
	  ○ What kind of feedback do you get from the health professionals?
	  ○ What education or instructions have you been given for monitoring your condition at home?
	  ○ How do you feel about monitoring your own health condition?
	  ○ If telemonitoring – how do you feel about using this technology?
	  ○ Does it help or hinder your routine?
	• What would make you seek medical help for your heart condition?
	  ○ Who would you contact?
	  ○ And how quickly would you do it?
	  ○ Have you ever done this? Tell me what happened
	• Have you been given instructions for what to do if your heart symptoms get worse?
	• How do you feel about having your condition monitored the way it is?
	  ○ What are the positives? (e.g. reassurance)
	  ○ Are there any downsides to it? (e.g. inconvenience, anxiety)
	• How would you feel if the health professionals looking after you said they wanted to change the way you are monitored? (e.g. frequency, daily weight, different types of tests, self-monitoring, telemonitoring, POC blood testing at the GP's surgery)

continued

TABLE 2 The CHF interview guide (16 new patient interviews conducted in 2015) (*continued*)

Topic	Questions

Self-management and lifestyle behaviours	• Have you ever been given any advice or education about how to look after your heart? (e.g. lifestyle changes, diet – salt reduction, taking exercise, quitting smoking, limiting alcohol)
	• Have you made any changes to your lifestyle because of your heart condition?
	  ○ If so, what changes and why? (e.g. imposed by physical limitations or through choice)
	• Have you ever attended a cardiac rehabilitation programme?
	  ○ Tell me about it. (Note: should include information and education as well as exercise)

Impacts of heart failure	Please tell me how your heart condition impacts on your life • What symptoms does it give you? (breathlessness, weight gain, ankle swelling, fatigue, urinary frequency at night, persistent cough, nausea, lack of appetite, confusion) • How does it affect your daily activities? (e.g. work, exercise, household tasks, mobility, climbing stairs vs. restricted to living downstairs, driving, air travel) • Does it impact on your sleep? (e.g. quality of sleep, need to sleep propped up on pillows or in a chair) • How does it impact on your family and social life? • What about your sex life? • Does it have any emotional impacts on you? • Does it make you sad, upset, anxious, depressed? • Have you discussed your feelings with anyone? • Have you been diagnosed with depression because of it? • Have you had treatment for depression? Tell me about it

What are your thoughts about the future?	• Do you think about what it might be like or how it might affect you?
	• Have any future treatment options been discussed?
	• Do you have any concerns about the future? Have you discussed them with anyone? Tell me about that
	• How do you cope with your heart condition?
	  ○ What helps you to live with it?
	  ○ Is there anything that gets in the way of you coping?
	• Do you feel you have enough support?
	  ○ Who supports you and how? (health professionals, social care professionals, family, friends, other patients, support groups, other)
	  ○ What impact does it have on friends and family?
	  ○ Do you have any equipment to help you? (e.g. mobility aids)
	  ○ Do you have any needs that are not being met?
	  ○ What are they and how could they be met?

Satisfaction with health professionals	How do you feel about the health professionals that are looking after you? • Do they talk to you in a way you can understand? • Have they given you enough information about your condition and its treatment? • If not, have you looked for information yourself? • What have you found helpful or unhelpful? • What things would you still like more information about? • Have the professionals involved you in decisions about your care and treatment? • Have they involved any close family members in discussions about your care and treatment?
And finally . . .	• Do you have any messages for health professionals who are looking after people like you? • Do you have any messages for other people with a heart condition like yours? • Or for families of people with a heart condition? • Is there anything else you would like to tell me about your heart condition or your health more generally?

ECG, electrocardiography.

TABLE 3 Patient interview sample characteristics

	CKD		CHF	
Characteristic	***n***	**%**	***n***	**%**
Sex				
Men	25	55.6	38	64.4
Women	20	44.4	21	35.6
Age (years) at time of interview				
< 40	1	2.2	3	5.1
40–49	1	2.2	5	8.5
50–59	7	15.6	11	18.6
60–69	5	11.1	17	28.8
70–79	26	57.8	13	22.0
80–89	4	8.89	10	16.9
90–99	1	2.2		
Recruited via				
GP	36	80.0	17	28.8
Support group/charity	5	11.1	17	28.8
Nurse			9	15.3
Consultant			4	6.8
Hospice			1	1.7
Snowballing	1	2.2	1	1.7
Other study	2	4.44	1	1.7
Social media	1	2.2		
Unknown			8	13.6

Questioning in the new interviews focused on patients' attitudes to monitoring: what they felt about the timing of visits, what they gained from the visit, what they understood about the purpose of monitoring and how they would feel about any changes in how monitoring is organised. We also explored attitudes to medication and decision thresholds as to when to seek medical attention. The new interviews were initially analysed without reference to the secondary analysis, to allow the coding structure to emerge from the data, rather than coding to predetermined codes. Codes concerning managing/monitoring of the condition and medication were examined in greater detail and coded more finely (*Table 4*). Each of the subcodes was then thematically analysed. Written analyses were prepared separately for the original and new data sets, before being combined.

Results

The original CHF interviews contained little material about monitoring the condition, as the study had pre-dated NICE guidelines on this topic. Our combined analyses of the original and new interviews were published online in 2016[76] as a major update and restructuring of the existing site, which included new topic summaries on the following: heart failure monitoring – check-ups with health professionals; access to health professionals between appointments; heart failure monitoring at home; and attitudes to heart failure monitoring. Key findings related to monitoring are summarised in the following paragraphs.

TABLE 4 Coded themes for the CHD analyses

Secondary analysis	Primary analysis of new interviews
Heart events or symptoms	Background to their heart condition and its treatment
Diagnostic tests and procedures	
Surgical procedures and angioplasty	
	Learning and understanding the heart failure diagnosis
Causes of heart problems	Causes
Information about heart failure	Information
Medication	Medications
What drugs	
Level of understanding	
Drug regimen and dose changes	
Adherence and self-management	
Side effects and interactions	
Complementary medicines or therapies	Complementary/alternative medicines and over-the-counter medicines and recreational drugs
Other	Oxygen treatment
Monitoring and access to professionals	Management of the condition
Health professional appointments and tests	Tests and check-ups with a health professional
Access between appointments and triggers to consult	Unplanned access to health professionals
Self-monitoring	Self-monitoring
Psychological impacts of monitoring	Attitudes towards
	Weight
	Blood pressure
	Oxygen saturation
	International normalised ratio
Remote monitoring of implanted cardiac devices	Telemonitoring
Other	
	Satisfaction with care
	Views about changes to monitoring
	Healthy lifestyle behaviours
	Physical activity and exercise
	Diet and weight
	Stress avoidance
	Smoking
	Alcohol
	Coping strategies or attitudes
Living with heart failure	Impacts of heart failure
	The future
Satisfaction with health professionals or the NHS	Support (from professionals, family, friends, peer support groups)
Other health conditions	Other medical conditions

Monitoring took place in primary or secondary care or a combination; care delivered by specialist nurses was particularly valued. Intervals between check-ups with a health professional ranged from 1 year to 1 week. Some people monitored their weight and blood pressure at home. A few interviewed in 2015 had experience of automated systems of monitoring such as telephone calls or texts; one had taken part in a telemonitoring trial. People with implanted cardiac devices and some of those with pacemakers had a machine at home for sending data downloads automatically to the hospital.

Having their CHF monitored provided people with reassurance that someone was keeping an eye on them and that test results were satisfactory. Current monitoring regimens were largely acceptable; a few expressed minor criticisms. Although many people had been told to contact a health professional if they had any concerns, and had done so, advice about when to seek help did not seem to have been given, other than for emergency situations. It had often taken a long time for the optimum level of medication to be achieved and unwelcome side effects were common. People said they disliked having to take medicines, but accepted that it was necessary.

Responses to questions about hypothetical future changes to monitoring regimens indicated that approval would be forthcoming provided the rationale was explained, in particular for changes to frequency for reasons other than a change in disease severity or stability. However, systemic changes of the professionals involved in heart failure monitoring could be problematic if patients had developed an especially trusting relationship with a particular professional. Self-monitoring would not be acceptable to all, but some people who were not already doing it would be prepared to do so, provided measurements were not required more frequently than their disease severity appeared to warrant. Equipment would need to be provided for some patients. Those with experience of telemonitoring of weight and blood pressure measurements found it acceptable. Home monitoring of implanted cardiac devices was valued by all those who had it. An increased reliance on blood testing in future would be acceptable, and POC testing in GPs' surgeries would be appreciated by people who become anxious waiting days or weeks for test results.

The chronic kidney disease patient study

Method

The sampling categories and interview guide were developed with help from an expert advisory panel (*Table 5*). We sought to recruit people who were having regular checks of their kidney function because they had stage G1–3 CKD. The Bristol-based researcher recruited participants entirely through GPs in the Bristol area, aided by service support costs. The Oxford-based researcher recruited nationwide using the usual range of methods for healthtalk studies (GPs, hospital consultants, advisory panel members, support organisations/charities, social media and snowballing through personal contacts) and also via the OxRen cohort study being conducted within the Oxford NDPCHS.[89] Forty-six people were recruited; one withdrew after interview. The stage of CKD was unknown for seven participants, 35 had stage G3, two had stage G2, and two had been recently referred to specialist care because of more advanced kidney disease, but could reflect back on their experiences of being monitored in primary care. See *Table 3* for sample characteristics.

To avoid participants learning about their diagnosis through taking part in the study, we had stipulated that health professionals should recruit only participants who had been told either that they had CKD or that their kidney function was being monitored. Given disagreement about the meaning of the term CKD, we described the topic of our research in recruitment literature as 'kidney health'. However, despite health professionals' assurances that they had told participants the reason why they were approached, it became apparent during interviews that some lacked awareness that their kidney function was impaired. To prevent these participants from learning of their CKD from the researcher, certain questions in the interview schedule were omitted or reformulated, and exploration of experience tended to focus to a greater extent on other comorbidities for this subgroup. The interview guide is presented in *Table 6*.

TABLE 5 The CKD advisory panel membership

Name	Position
Dr Jeremy Horwood	PI, School of Social and Community Medicine, University of Bristol (chairperson)
Dr Kristina Bennert	Qualitative Researcher, School of Social and Community Medicine, University of Bristol
Dr Tom Blakeman	Co-applicant, National Institute for Health Research Clinical Lecturer in Primary Care
Dr Fergus Caskey	Renal Specialist, North Bristol NHS Trust
Ms Di Croft	Specialist Diabetes Nurse in Primary Care, Oxford
Dr Julie Evans	Senior Qualitative Researcher, HERG, University of Oxford
Professor Gene Feder	Co-applicant, Professor of Primary Care, School of Social and Community Medicine, University of Bristol
Dr Kathryn Griffith	Royal College of General Practitioners Clinical Champion for Chronic Kidney Disease, University of York
Ms Sarah Griffith	Diabetes and Hypertension Nurse in Primary Care, NHS Bristol Clinical Commissioning Group
Dr Daniel S Lasserson	GP and Senior Clinical Researcher, University of Oxford
Dr Louise Locock	Co-applicant, Deputy Research Director, HERG, University of Oxford
Ms Fiona Loud	Patient Representative, Director of the Kidney Alliance
Mr Andy Williamson	Patient Representative, Kidney Patient Guide Forum Moderator

TABLE 6 Chronic kidney disease patient interview guide (kidney checks in primary care)

Topic	Questions
Narrative section	
Opening question: as you know, we are interested in hearing about your experiences of having regular checks of your kidney function, but, in order to provide some context for that, perhaps you could start by telling me about your health in general, any conditions you have been diagnosed with and how they affect you, any treatments you are having, and how the kidney function checks fit into the overall picture?	
Supplementary question	
Thank you. Now please could you tell me about your kidney checks. The sorts of things I'd like to hear about are how the subject of your kidney function first came up, how often you are checked and by whom, what the checks consist of, what you are told about the results, and how you feel about having these checks. Don't worry if you forget to talk about some of these things: when you have finished, I will ask you questions to fill in any gaps.	
Semistructured questioning as necessary	

General health	• Do you experience any symptoms from any of your health conditions?
	• If so, what, and how do they affect you? (Note: symptoms of CKD should occur only in stages G4–5: tiredness, difficulty concentrating, itchy skin, swollen ankles, breathlessness on exertion, poor appetite and weight loss, nausea)
	• Are you having any treatments for any of your health conditions?
	  ○ If so, what and how often? (e.g. blood pressure medications, insulin, statins, other)
	• How easy is it to take your medication as it is prescribed? (Prompts: what helps or hinders?)
	• How does being on medication affect you, your family or your social life?
	• Do you experience any problematic side effects?
	  ○ If so, have you sought help for these and what was the outcome?
	• Were you involved in the decision to have this treatment?
	• Has it changed the way you live your life … can you tell me about that?

TABLE 6 Chronic kidney disease patient interview guide (kidney checks in primary care) (*continued*)

Topic	Questions
	• Have you been advised to lead a healthier lifestyle? (Prompts: by whom doctor/nurse/specialist?, format?) (Prompts: quit smoking, healthy diet including low salt, weight loss, physical activity, less alcohol) ○ If so, have you managed to do this, and how? How have those changes affected you?
	• Do you take any over-the-counter medications or use any complementary therapies?
Introducing kidney function	• Just talk me through what happened when you went to your GP and they first spoke to you about your kidneys • Who carried out the tests: GP, nurse? • Was it part of a routine testing? (Prompts: NHS Health Checks or because of symptoms) • What was your understanding then of why the nurse/doctor wanted to test your kidneys? (Prompts: CKD diagnosis, the term 'chronic', risks to future health, comorbidities, causes) • How did you feel about it? • I know it might be difficult to remember, but it would be helpful to know: what went through your mind when the nurse/doctor told you about your kidneys? • What kind of questions did you (your son/daughter/husband/partner) ask the doctor about your kidneys?
Information	• It's always helpful if people tell us about the kind of information they have been given – what worked and what did not and what kinds of things would be helpful … • What information were you given? • Did you ask for any additional information? ○ If so, what and from whom? Was it useful? What information were you looking for?
	• Did you look for any additional information elsewhere? ○ If so, what, and from where? Was it useful? What information were you looking for? (Prompts: other people's experiences; websites, social media, etc.)
	• Has your understanding changed over time? • What does it mean to you to have this issue with your kidneys? (Prompts: pros and cons of knowing – anxiety, adopting illness role or not – liminal state, medicalisation/pathologisation) • Who have you told about it and how did they react? (Prompts: family, partner, friends, colleagues) • Is there anyone you have not told? ○ If so, why?
Initial knowledge	• Before this happened to you, did you know that people could have these kinds of problems with their kidneys? • What did you understand or know about kidneys at that point? • Has anyone else in your immediate family had kidney issues? • I wonder if you have any thoughts about why you have got kidney issues?
Kidney checks	• How was the topic of kidney checks first raised? • What tests do you have, how often and where? (Prompts: bloods: creatinine/eGFR, urine, blood pressure, ultrasound scan, other) ○ (For each test:) what is/was it like having that test? (Prompts: do you mind it, pain/discomfort, anxiety, do the staff put you at ease?)
	• Do you ever have 'fasting blood tests', where you have to not eat before the blood is taken? ○ If so, how do you feel about having to do that?
	• How do you find out the results of each test? • Are the test results explained to you? ○ If so, how and by whom?
	• Do you understand what the results mean? • What are the staff like? (Prompts: what have they done well; what has been less positive?) • Do you get anything positive out of the visit? (e.g. a chance to ask questions, gain reassurance) • What are the downsides for you? (e.g. worry, reminder of their CKD, interferes with lifestyle)

continued

TABLE 6 Chronic kidney disease patient interview guide (kidney checks in primary care) (*continued*)

Topic	Questions
	• How do you feel about the frequency of the testing? (Prompts: too often, not often enough; just right) • How would you feel if your doctor wanted to change the way you are monitored? (Prompts: different tests or frequency of testing) • How would you feel about 'point-of-care testing' (i.e. instant results)? • Are there ways in which services could be improved for you?
Impacts	• What is it like to live with these health problems? (CKD and related comorbidities) (Prompts: has it affected your day-to-day activities; work; finances; relationships; insurance; have you had to make changes to the way you live?; Has it impacted on family and friends?; Genetic risks?) • What helps you to live with your condition(s)? • What makes it harder to live with your condition(s)? • What solutions, if any, have you found to deal with problems? • Is there anything else you can think of that could make life better for other people with similar problems?

Support	• Do you feel you have enough support for dealing with your condition(s)? (Prompts: practical; emotional)
	  ○ If yes, who supports you, and how?
	  ○ If no, what support would you like and from whom?
	• Do you know anyone else who has their kidneys checked regularly like you do? (e.g. through a support group for a comorbidity; other patients they meet at clinic)
	• Would you like to know about other people's experiences of kidney checks/disease?
	• Is there anything relating to kidney checks that you feel you do not know as much as you would like about? (Either that you have never asked or feel you have not had an acceptable/understandable answer to)
	• What do you think about kidney checks for people like you? Do you think it is a good or a bad thing, and why?
	• Do you think there is enough public awareness of kidney problems like yours?
	• How could people be made more aware of it?

Future	• What impact do you think your kidney problems might have on your life in future? • Do you have any concerns about this? • Have any other treatment options been discussed for the future? (e.g. other medications, dialysis, transplant) • If so what, and how do you feel about that?
Messages to others	• What messages would you give to other people who are having their kidney function monitored? • What messages would you give to partners and family of people with kidney problems? • What messages would you give to health professionals looking after people like you?
Final questions	• We have reached the end of our interview. Is there anything else you would like to add that we might have missed out? • Why did you decide to take part in this interview study? • [Can provide useful quotations for the value of www.healthtalk.org (accessed 5 May 2020) for launch publicity]

Note
For patients who have been told that they have mild-to-moderate CKD only (stages G1–3; no dialysis or transplant) or that they are on a CKD register, we should already know from their reply slip for how long they have been monitored and what comorbidities they have.

Results

The main findings were published online in 2015[31] as 'topic summaries', illustrated with extracts from the interviews. Topic summaries about monitoring (check-ups in general practice and hospital; diagnosing problems with kidney health; tests used to monitor kidney health; receiving and making sense of test results; and attitudes towards monitoring kidney health) were complemented by summaries about the diagnosis and its disclosure, information and support needs, and looking after kidney health. Key findings are summarised in the following paragraph.

A gap was revealed between what health professionals seek to explain about CKD and what patients may understand. Primary care professionals often avoided using the term 'CKD' when talking to patients with early-stage kidney impairment in an attempt to avoid causing unnecessary anxiety. Patients' accounts of receiving information about their kidney health echoed the phrases described by health professionals. However, patient interpretations showed some of these phrases to be unhelpful, raising further questions and adding to, rather than diminishing, initial concerns. The use of phrases such as 'kidney damage' or 'kidney failure' could be frightening, and the term 'chronic' was sometimes misinterpreted as meaning serious, whereas a description of the decrease in kidney function as a percentage or stage seemed less alarming. However, the exact meaning of the test results was often unclear, and those who were told their CKD stage did not always understand what this meant. For some patients, it could be difficult to understand that they had been diagnosed with CKD when they did not experience symptoms. Attempting to reassure patients that their kidney impairment was nothing to worry about, without providing explanatory information about the condition, could leave patients concerned and wanting to know more about possible causes, the meaning of test results and whether or not they could do anything to prevent further decline.

The focus group study with health professionals

Method

With approval from the University of Oxford's Central University Research Ethics Committee (reference number R49627/RE001), we recruited individual GPs and practice nurses from Oxfordshire, and CHFN teams from the wider Thames Valley area (because the numbers were small). CHFN team leads were contacted and invited to forward the study information to their members. GPs and practice nurses known to us through other studies run by the NDPCHS were invited to participate. GP colleagues from the NDPCHS were invited and asked to forward details to their practice nurses. Members of the Oxfordshire practice nurse forum were also invited.

Recruitment proved difficult, resulting in few participants of all professional types, exacerbated by people dropping out at short notice because of unforeseen circumstances. Sixteen people participated in four focus groups. One was held with each of two teams of CHFNs as part of their regular team meeting, another with GPs, held at the NDPCHS, with light refreshments provided. We succeeded in recruiting enough practice nurses for a fourth group only by offering a complimentary meal at an Oxford college. *Table 7* presents the participant characteristics.

Before each session, the participants signed their consent, including to be video-recorded. As an 'ice-breaker', practice nurses were asked to explain the ways in which they were involved in managing

TABLE 7 Focus group participant characteristics

Characteristic	CHFNs	GPs	Practice nurses	Total
Groups held (*n*)	2	1	1	4
Participants (*n*)	7	5	4	16
Men (*n*)	0	1	0	1
Age range (years)	41–49	46–57	53–72	
Minority ethnic participants (*n*)	3	0	0	3
Years in practice (range)	< 1–10	18–23	3–38	

patients with CKD or CHF; CHFNs and GPs were asked to complete the following sentence: 'In managing patients with CKD or CHF, NICE (National Institute for Health and Care Excellence) guidelines are helpful because . . .'. Further questions and prompts followed to elicit how NICE guidelines affected real-life clinical management and any difficulties in applying them, before discussing how the monitoring of these conditions might be improved. Short pre-recorded video presentations stimulated debate on potential impacts of future developments in monitoring arising from the wider research programme. These concerned the possible use of the term 'kidney age' when talking to patients about CKD (GPs and practice nurses only), monitoring CHF patients' NPs to guide treatment, and use of a POC device for measuring NP. Each session was designed to last 1 hour and closed with participants feeding back what, if anything, they had learned.

Focus groups were audio- and video-recorded and the research assistant's notes were expanded while listening to the recording to form a rough anonymised transcript. A thematic framework analysis was structured around the main areas of questioning and any emergent themes. Selected quotations were fully transcribed for presentation; hesitations and overlapping speech were removed to aid readability. Data collection and analysis proceeded in parallel so that early findings could inform questioning in the subsequent focus groups. Video-recordings were used to examine non-verbal cues and interactions between focus group members and how these affected the content.

Results

National Institute for Health and Care Excellence guidelines

Community heart failure nurses were fully cognisant of the NICE guidelines for managing people with CHF and used them on a daily basis to guide their care. However, not all patients could be treated strictly according to the guidelines, either because of competing treatment targets for comorbidities or because patients could not tolerate certain medicines. CHFNs therefore used their clinical knowledge, skills and close links with cardiology consultants to adapt the recommended treatments to suit individual patients.

Community heart failure nurses sometimes found it difficult working with GPs, who were not always up to date with NICE guidance and appeared to use different thresholds for blood pressure or kidney function when altering medication. When communicating with GPs about specific patients, CHFNs said they had taken to explaining that their proposed treatment plan accorded with NICE guidelines, a strategy that usually resulted in the GP's agreement:

> *Sometimes GPs are not that up to date on certain things, but usually when you say, 'These are the NICE guidelines', they usually follow suit. But sometimes that can be a bit challenging.*
>
> *CHFN 07*

The GPs all confessed to being unfamiliar with the latest updates to NICE guidelines for either CHF or CKD, or both, arguing that work pressures did not allow time to read these for all conditions. The NICE website was considered confusing and difficult to navigate, and GPs were more likely to learn about patient management recommendations from other sources, such as the Clinical Commissioning Group or QOF alerts.

Some aspects of NICE guidelines that GPs were familiar with were perceived to be impractical and did not reflect real life in general practice, although one participant pointed out that such aspirational guidelines could be used to lever change at commissioning level. On the current CKD guidelines,[11] specifically, there was confusion about when albumin–creatinine ratios should be requested from the laboratory and how the results should be interpreted and acted on.

One practice nurse said she liked to read NICE guidelines, but agreed with the others that, although they would like to understand the evidence base for management strategies, most practice nurses do

not have time to read NICE guidelines and they tend to work according to QOF targets and local protocols unquestioningly, rather than to national guidelines. However, one practice nurse said she occasionally consulted NICE guidelines for specific treatment advice.

Monitoring patients with chronic heart failure

Although there was no structured recall for CHF patients via the QOF, and practice nurses did not see patients specifically about their heart failure, both GPs and practice nurses saw many patients with CHF in clinics for other long-term conditions. The practice nurses primarily saw patients about their diabetes, hypertension or respiratory disease and were not expert in CHF. Practice nurses suggested that management of CHF could possibly be improved by greater provision of education to patients about lifestyle to try to prevent the condition from developing in the first place, or to optimise their health once they had it, and about what to do when things go wrong.

The GPs' discussion on this topic centred on their uncertainties about how they should manage CHF patients. GPs were unsure what tests they should be doing and when, and how, to interpret and act on the results. They did not know how to identify opportunities for intervention that might benefit the patient, such as cardiac resynchronisation. They would welcome specific guidance from specialists about how to manage individual patients discharged from secondary care:

> *So an interesting primary care question is: how do we understand what the threshold or the point where we could, would or should be referring these people back for more echoes [echocardiography] or at what point might they benefit? Because if the burden of managing the vast majority of people with heart failure is with us and there is an intervention that's effective, but we don't know how to identify when they need to go back, that strikes me as quite important.*
>
> *GP01*

General practitioners sometimes felt criticised by cardiologists for up-titrating a patient's medicines too slowly, when, in reality, this process could be challenging because of patient factors beyond their control. They also struggled to manage patients who had CHF with preserved ejection fraction, who are not seen in Oxfordshire by CHFNs. By contrast, the CHFNs in one group said they accepted patients with all types of CHF. One GP mentioned developments in automated RM of CHF patients, but believed that few of their own patients would take to using such technology. However, CHFNs who used these technologies found that their more elderly patients got on well with this method of monitoring and felt reassured that someone was keeping an eye on them.

Community heart failure nurses in one group felt that wider use of telemonitoring was one way in which heart failure monitoring could be improved. They would also welcome Skype™ (Microsoft Corporation, Redmond, WA, USA) clinics that would enable patients to remain at home, and joint clinics with respiratory and renal specialists and pharmacists. They would also like communication between professionals to be improved by means of shared information technology systems across administrative boundaries, instead of the current fragmented arrangements, and more coherent ways of working among CHFNs nationally:

> *Having a system that we could all just write on, one system, would be lovely. I mean it's like we have a system, and yes that talks to community matrons, district nurses and mental health, but it doesn't talk to the COPD [chronic obstructive pulmonary disease] team or the GP.*
>
> *CHFN 07*

Community heart failure nurses in the other group said their work could be made easier if they had more staff with which to share their case load, especially as they typically became involved in dealing with non-CHF issues, being the only professional visiting the patients at home.

Potential future use of natriuretic peptide measurements in chronic heart failure monitoring

Only one of the practice nurses was familiar with NP tests and had used them for diagnostic purposes; the others had never heard of them and queried how using NP measurements for monitoring might change patient management. One GP was attracted by the idea of a measure that could potentially show that they had optimised a particular patient's treatment. Other GPs could not see where monitoring a patient's NP would fit into their management:

> *So the question is where would the [BNP] test sit? How often would it need to be done? What would it let us do that we're not doing now? What could it help us do better from a patient point of view?*
>
> *GP01*

Both GPs and CHFNs, and one of the practice nurses, recognised NP as a useful diagnostic test for CHF and to rule out other causes of breathlessness such as chronic obstructive pulmonary disease. However, the CHFNs could see no benefit of measuring NP as part of routine monitoring. Changes in NP were believed to reflect the severity of symptoms in most patients and CHFNs believed in managing their patients according to symptoms, not numbers. It was unclear how knowing the NP would alter their management in most cases, and telling a patient that their NP was rising could negatively affect a patient's well-being:

> *I'm not convinced it's going to change your treatment, whatever the reading is going to be. Not like a renal function or a haemoglobin or, you know, those kind of things would change your management maybe. But pro-BNP I don't think would change that.*
>
> *CHFN 06*

> *But with people that you know have got no other comorbidities, have got major heart failure anyway, what are numbers going to tell us? I mean, our consultants are quite anti-numbers, aren't they, anyway. You know, they'll say 'Go on symptoms, don't go on that their blood pressure's 80 systolic or their renal function's 300; go on how they're feeling and what we need to do'. [. . .] Actually, I think we get very fixated on numbers, and it might be more detrimental to patients. 'Yes, you know, your BNP was 4000 last week, oh damn, it's 8000 this week, oh it's getting worse.' What's that going to tell them, really? I mean, it tells us their heart failure is getting worse but we can probably see that by looking at them.*
>
> *CHFN 07*

Furthermore, all groups believed that the cost of the test (both financial and in terms of professionals' time and extra blood samples required from the patient) would outweigh any potential benefits. One CHFN suggested that the money could be better spent on providing cardiac rehabilitation for people with CHF, which had proven benefits. The practice nurses debated the relative merits of educating patients to self-monitor their condition, such as by regular weight measurements, and to seek help if it changed.

One GP raised the issue of inaccurate NP measurements resulting from blood samples taken from surgeries that were far from the laboratory, which led to a suggestion that a POC device to measure NP could be a useful alternative for GPs. A CHFN pointed out that use of a NP POC device in general practice could speed up diagnosis because their laboratory ran the NP assay only once per week. A practice nurse suggested that using a POC device for monitoring NP could prevent a patient being 'over-diuresed' while waiting for a laboratory test result to arrive. However, CHFNs would be reluctant to add a POC device to the already large collection of equipment that they have to carry when visiting patients, because they see no value in its routine use. One added that they would also like to know a patient's renal function at the same time as their NP before changing any medicines.

Talking to patients about chronic kidney disease

In both the GP and practice nurse groups, the problem of terminology about kidney function was raised spontaneously before the researcher showed the presentation about the suggested alternative term 'kidney age'. Both groups said that CKD needed a new name, and the nurses mentioned that kidney function naturally declines with increasing age:

> *And it's difficult because I hate the term 'chronic kidney disease'. I've found it difficult to navigate a way through those conversations constructively with patients.*
>
> *GP01*

After watching the presentation, the practice nurses said that they liked the suggested term 'kidney age' because it demedicalised CKD, thereby making it easier to discuss with patients, and they drew parallels with the existing concept of lung age. The opportunity to demedicalise kidney impairment through embracing the term 'kidney age' served to reinforce the view of one practice nurse that people should not have a part of the normal ageing process monitored unless it could be reversed:

> *I'd much rather have that terminology of saying that your kidney age . . . It's like the lung age, isn't it, the same sort of conversation. Which isn't too upsetting because you're not telling them they've got a disease, you're telling them that their kidneys are older than they should be. I think that's it. Reasonable discussion with the patient. And then what can we do, if anything, about your lifestyle that would facilitate it lessening the progression, or making things better, or looking at your drugs?*
>
> *Practice nurse 02*

The nurses debated what lifestyle and other interventions might help slow or reverse kidney impairment, such as optimising treatment for diabetes, CHF and hypertension; avoiding prescribing medicines that can damage kidney function; quitting smoking; losing weight; and reducing dietary intake of alcohol or salt. However, none was sure if any of this would make a difference. Some practice nurses felt that monitoring kidney function could help to identify factors that could precipitate a rapid decline to genuine kidney disease. One drew parallels with her work on respiratory disease.

Although all disliked the term CKD and wanted a workable alternative, the GPs were not convinced that 'kidney age' was the answer to the current communication problem. 'Kidney age' was potentially a helpful concept for doctors to understand declining kidney function, and it might mean that they intervened less as a result, but they were not sure that they would want to use it when explaining the condition to patients. It was suggested that, unlike 'lung age', whereby patients can be motivated to quit smoking to improve their lung function, there was nothing equivalent that the patient could do to improve their kidney function, except perhaps helping to optimise their blood pressure control. Therefore, telling a patient that their kidneys are considerably older than their biological age could cause unnecessary anxiety:

> GP03: *And I think that use of 'kidney age' reminds me of 'lung age', which is possibly what it's based on. But at least, with 'lung age', on the whole you are using it as a motivational factor, aren't you, for smoking cessation, and it is pretty powerful; it does shock some people in a way that seems surprising to a medical mind when you think 'I can tell you all this time this and that and this and that, and none of it made any impact till I told you you had a lung age of 75 when you're 50'. But it just goes to show the terrible assumptions we make and how you have to explain things in terms that people understand. But there's a point to that, you're telling . . . Whereas, in this situation, you're saying, 'Your kidneys have aged darling', and . . .*
>
> GP05: *Your lungs can look 10 years younger just as your face does when you . . . Yeah, all those . . . But actually, your kidneys, there's something much more frightening. [. . .] So we think it needs a different name but not that one.*

When asked if they could suggest alternatives to 'kidney age', the practice nurses suggested that kidney function could be measured on a scale of 'kidney health' as opposed to 'kidney disease', so as to adopt a more positive emphasis. One GP said they liked to use the term 'kidney reserve' because it gave a sense of what you could do with a certain level of kidney function, and it seemed less emotive than 'kidney age'.

Interactions between participants and non-verbal cues

In both CHFN groups, an element of peer pressure to agree to the session being video-recorded was apparent, and one nurse was teased by her team leader for being uncharacteristically quiet during the discussion. In both groups, it was difficult to keep the discussion flowing, the team lead spoke the most and there was a tendency for the participants to agree with each other. Most of the conversation was directed at the researcher rather than to each other.

The GPs and practice nurses appeared happy to agree to the video-recording. Four of the five GPs were also academics and knew each other. Two of the practice nurses worked in the same practice. Discussion in the GP and practice nurse groups was more animated than in the CHFN groups, proceeded with ease and lasted longer; the researcher interjected only to change the topic. There were intermittent bouts of laughter and multiple interruptions of each other's speech. However, when one particular GP interrupted, all the other participants stopped talking and paid attention. This GP appeared to be considered more expert because of their involvement in commissioning. Discussion in the practice nurse group was dominated by one particular nurse, although it did not appear to prevent others speaking. Apart from the opposing opinions among the practice nurses about the relative merits of monitoring kidney function, consensus among participants in each group was high. All the participants sat in a relaxed manner throughout and there were few instances of body language that could suggest unease, dissent or lack of engagement.

Limitations

Recruitment took place across just two counties and participant numbers were small, so the views expressed cannot be regarded as representative of these professions as a whole. The focus groups in which both CHF and CKD were discussed (GPs and practice nurses) over-ran the time allowed, which was insufficient for in-depth discussion of all the relevant issues.

Conclusions

The organisation of heart failure services currently varies across administrative boundaries, even within counties. In one area, the CHFN team dealt with patients with all types of CHF; in the other areas, CHFNs saw patients with left ventricular systolic dysfunction only. Information technology systems are fragmented, so professionals cannot access information about patients when they are treated in a different area. More uniform service provision and coherent information technology systems could increase the efficiency of patient management.

Community heart failure nurses use NICE guidelines as an essential tool in managing their patients and in eliciting support from individual patients' GPs for proposed treatment plans. GPs are uncertain how to manage patients with CHF, yet they do not have time to read updated NICE guidelines, which could provide some of the information they lack. GPs would like to receive specific guidance from specialists about how to manage individual patients. CHFNs who offer this kind of advice say it is well received by GPs. Practice nurses do not routinely read NICE guidelines, their work being driven by QOF targets and local protocols. Because there is no structured recall in the QOF for CHF patients, GPs and practice nurses tend to see them for medication reviews and in clinics for other long-term conditions, rather than specifically about their CHF. So although these patients receive relatively intensive monitoring,

it is not specifically for their CHF, and GPs do not think about monitoring for this condition in isolation. Primary care staff need to be better educated about how to manage CHF patients.

Patients often felt frustrated at the time it took to up-titrate their CHF medicines, and GPs felt pressured by specialists to do it more quickly than was possible in practice.

Patients with CHF are amenable to possible future changes in monitoring regimens, provided the rationale for change is explained to them. Although all groups of professionals recognised that a NP POC device could be useful in general practice to speed up diagnosis of CHF and to produce more accurate test results, measuring NP as a regular part of patient monitoring was not seen as adding anything useful to what the professionals already did in managing their patients. Furthermore, CHFNs would be reluctant to alter patient management on the basis of a NP measurement without also knowing a patient's renal function. Professionals also considered the NP test expensive and potentially a waste of scarce resources. Further evaluation of the evidence around NP monitoring is needed to establish what changes in routine management could lead to patient benefits.

Although CHF patients are well aware of their condition and commonly felt reassured by having it monitored by professionals, improvements are needed in the ways in which GPs communicate with patients about CKD, which is a much less readily understandable 'diagnosis'. This finding contributed to a mixed-methods article that calls for a rethink in how doctors talk to some patients with reduced kidney health, replacing the term 'CKD with different bands of kidney age.[45]

General practitioners and practice nurses were keen for CKD to be given a different name. Practice nurses felt that using 'kidney age' would facilitate conversations with patients because it demedicalised the condition, and they would be keen to discuss lifestyle issues that might slow the decline. By contrast, GPs were not keen on the proposed term 'kidney age' because of concerns that it could still cause unnecessary anxiety if a patient's kidney function had declined beyond what was normal for their age, believing that there was little, if anything, that could be done to slow or reverse the decline.

Appendix 10 Understanding tensions and identifying clinician agreement on improvements to early-stage chronic kidney disease monitoring in primary care: a qualitative study

Simmonds *et al.*[30] https://doi.org/10.1136/bmjopen-2015-010337

Appendix 11 Kidney age, not kidney disease

Stevens *et al.*[45] https://doi.org/10.1503/cmaj.170674

Appendix 12 Review of economic models of chronic kidney disease

Introduction

Monitoring and management of CKD aims to reduce the incidence of cardiovascular complications and slow the progression of kidney disease.[11] To fully assess the benefits and costs of CKD monitoring, a long-term model of the disease over the duration of a patient's lifetime is required. We reviewed the literature to identify existing cost-effectiveness models among patients with CKD that could be suitable for such an assessment.

Methods

The review focused on the models that could potentially be used specifically to evaluate cost-effectiveness of eGFR monitoring in the context of current clinical guidelines.[11,43,90] Therefore, a lifetime cost-effectiveness model was included only if (1) the target population was relatively non-specific (e.g. models aimed at CKD in type 1 diabetes or patients with secondary hyperparathyroidism were excluded), (2) CKD stages were defined using eGFR (i.e. not exclusively based on proteinuria status), (3) at least two distinct pre-RRT states were included (e.g. models with states 'pre-RRT' and 'RRT' were excluded) and (4) incidence of important cardiovascular events was modelled, and could support the implementation of cardio-protective treatments (e.g. statins, blood pressure-lowering medications, antiplatelets/anticoagulants).

A pearl-growing strategy[91] was chosen instead of a standard systematic review approach to more efficiently complete the review. The decision was based on a previous experience of an in-house review of models of CKD progression (unpublished), which resulted in tens of thousands of citations, the vast majority of which were not relevant. First, a set of key studies ('pearls') was identified by the authors using their previous experience and two published systematic reviews.[92,93] The reference lists and citations of each included study were reviewed, with relevant papers included, classified as new pearls, and the search repeated for another iteration, until no more relevant papers were identified. To ensure that no important manuscripts were missed, a scoping search was performed in Google Scholar (using the search line "cost-effectiveness 'chronic kidney disease' progression"), followed by a review of references (including those listed as excluded and original cost–utility analyses) in the relevant (health) economics sections of the NICE clinical guidelines for CKD.[11] All eligible published studies were included, with no restrictions on search databases or year of publication. The search was performed in January 2016 and updated in January 2019. Because the aim of the review was to identify all key studies, rather than to be exhaustive, a formal protocol registration was not sought.

A set of criteria was developed to help gauge model suitability for the research question, namely assessment of cost-effectiveness of CKD monitoring in the UK general primary care population. The criteria, based on authors' previous experiences in disease modelling,[36,94–96] included questions on generalisability of the model target population to that in UK primary care (i.e. whether or not patients with an eGFR of 60–90 ml/minute/1.73 m^2 were included), alignment of the modelled cardiovascular outcomes and treatment pathways with those in the clinical guidelines [i.e. whether or not the model enables implementation of the effect of antihypertensive, low-density lipoprotein- (LDL-) lowering and antiplatelet interventions], separation of RRT modalities to allow for their different health-care outcomes and costs (i.e. dialysis and renal transplantation), and model validation. For each model, information on each criterion, as well as model identifier, data sources used for populating the model and brief description of the model structure, was extracted (IS) and summarised in a table.

Results

Four suitable key studies ('pearls') were identified at the first iteration[32–36] in 2016–17; the review of reference lists and citations of the included studies, a scoping search in Google Scholar and review of the NICE clinical guideline did not yield further eligible studies. When the searches were repeated in January 2019, one additional newly published study was identified,[37] and no further studies were identified by iterating the search. Therefore, five long-term cost-effectiveness models, potentially useful to assess CKD monitoring, were included in the review.

Detailed characteristics of the included models are presented in *Table 8*. Of the five models, two were developed to assess the cost-effectiveness of CVD prevention interventions (e.g. statins) in CKD,[32,36] two were developed in the context of screening for CKD/proteinuria in the general population[33,34,37] and one aimed to accommodate both types of interventions.[35] Only one model targeted patients with mildly reduced renal function (eGFR of $\geq$ 60 ml/minute/1.73 m^2), which constitutes the bulk of the population with renal impairment in a primary care setting,[37] although patients with an eGFR of 60–90 ml/minute/1.73 m^2 were not separated from those with an eGFR of $\geq$ 90 ml/minute/1.73 m^2.

Parameters of the models were mostly collated from published literature and/or derived from different data sources, with only one model[36] based largely on individual patient-level data. Three models separated the ESRD state into dialysis and renal transplant states,[35–37] which are associated with different outcomes and costs. All models included validation of their performances. Two models enabled implementation of lipid-lowering medications, such as statins;[32,36] and four models enabled implementation of blood pressure-lowering medications, such as ACE inhibitors or ARBs[33,36,37] (although, in one of these, the medications were assumed to affect CKD progression only, rather than incidence of cardiovascular events directly[33,34] and implementation of treatment pathway was unclear in another model[35]). Only one model considered heart failure as an end point, but it was unclear how the treatment effect on heart failure, as well as the impact of this treatment on other transition probabilities, were implemented.[35] None of the models satisfied all suitability criteria (*Table 9*).

Discussion

None of the identified models included the key elements required for the assessment of cost-effectiveness of monitoring strategies in UK primary care in the context of current clinical guidelines. Therefore, it was decided to develop a new cost-effectiveness model to support the evaluation of CKD monitoring. A possible limitation of the review is employing the pearl-growing strategy instead of performing a comprehensive systematic search. However, given the checks performed and our concurrent involvement in CKD modelling research over a number of years and awareness of available relevant data, we are confident that we have not missed relevant studies.

TABLE 8 Summary of identified cost-effectiveness models in CKD

Model identifier	Target population	Modelled interventions, cardiovascular end points and treatment pathways	Modelled CKD stages	Modelled costs and quality-of-life utilities	Data sources	Structure	Validation
Erickson *et al.*,[32] 2013. *Cost-effectiveness of statins for primary cardiovascular prevention in chronic kidney disease*	Patients with CKD stage G3a, G3b or G4 with no previous cardiovascular event	Statin therapy. The intervention is assumed to affect directly the incidence of cardiovascular events (myocardial infarction, stroke). In a sensitivity analysis, the intervention is also assumed to affect CKD progression (and hence, indirectly, incidence of cardiovascular events)	CKD stage G3a, CKD stage G3b, CKD stage G4, CKD stage G5 (includes RRT)	• Costs: yes, health-care costs for each disease state and interventions' potential side effects • Utilities: yes, quality of life for each disease state; decreases for cardiovascular complications and interventions' potential side effects	Estimates of all parameters were based on published data (Framingham equations; studies in CKD; USRDS)	Lifetime Markov model with a 3-month transition cycle applied to simulated patients with predefined sets of baseline characteristics. Patients progress through modelled CKD stages using constant annual GFR decline. Probability of cardiovascular events and death depend on patient's CKD stage. Cost and quality depend on patient's CKD stage and CVD history. Potential adverse effects of statins are also implemented	Yes: model results were compared with US life tables by age, sex, CKD status and hypertension. Alternative assumptions (e.g. different speed of GFR decline, further potential adverse effects of statins) were explored, and all model inputs were varied in sensitivity analyses
Go *et al.*,[37] 2017. *Cost–utility analysis of the National Health Screening Program for chronic kidney disease in Korea*	General population; results also stratified by person's hypertension and diabetes status	CKD screening. The intervention is assumed to affect prescription of ACE inhibitors, intensive glycaemic and/or blood pressure control. This, in turn, directly affects incidence of cardiovascular events	eGFR of $\geq$ 60 ml/minute/1.73 m^2 (including no CKD, CKD stages G1 and G2), CKD stage G3, CKD stage G4, CKD stage G5 kidney transplant, haemodialysis and peritoneal dialysis	• Costs: yes, costs of disease states (from societal perspective) • Utilities: yes, health state-specific utilities	All model parameters were derived from published data from large cohort studies in the Korean population, claims data or literature from other countries	Lifetime Markov cohort model with an annual transition cycle applied to a simulated cohort. Patients' progress through CKD stages with transition probabilities depending on patient's starting	Yes: model's prevalence of each health state was compared with national statistics

continued

TABLE 8 Summary of identified cost-effectiveness models in CKD (*continued*)

Model identifier	Target population	Modelled interventions, cardiovascular end points and treatment pathways	Modelled CKD stages	Modelled costs and quality-of-life utilities	Data sources	Structure	Validation
		(myocardial infarction, stroke) and CKD progression and, indirectly, incidence of cardiovascular events				CKD stage, hypertension and diabetes status. Probability of cardiovascular events depends on patient's CKD stage, and complications such as hypertension and diabetes	
Hoerger *et al.*,[33] 2010. *A health policy model of CKD: 1. Model construction, assumptions, and validation of health consequences* Hoerger *et al.*,[34] 2010. *A health policy model of CKD: 2. The cost-effectiveness of microalbuminuria screening*	General population; results also stratified by person's hypertension and diabetes status	Screening for microalbuminuria. The intervention is assumed to affect prescription of ACE inhibitors or ARB treatments. This, in turn, is assumed to affect micro- to macroalbuminuria transition, mortality, CKD progression, and, indirectly, incidence of cardiovascular events (stroke, coronary heart disease)	No CKD, CKD stage G1, CKD stage G2, CKD stage G3, CKD stage G4, CKD stage G5, ESRD (all modalities combined)	Costs: yes, health-care costs of each disease state, CKD complications and risk factors Utilities: quality-of-life utilities for each disease state; quality-of-life decrements for CKD complications	Estimates of all model parameters were taken from the literature (e.g. Framingham equation), CKD expert panel or derived using data from NHANES and Medicare claims	Discrete-state microsimulation with annual transitions applied to a simulated cohort of patients. Patients progress forward through CKD stages according to their eGFR decrease. It is also possible to progress from micro- to macroalbuminuria. Probability of cardiovascular events depend on patient's risk factors and CKD stage	Yes: for each CKD stage, model-predicted CKD prevalence was compared with that reported in external studies (NHANES, USRDS)

Model identifier	Target population	Modelled interventions, cardiovascular end points and treatment pathways	Modelled CKD stages	Modelled costs and quality-of-life utilities	Data sources	Structure	Validation
Orlando *et al.*,[35] 2011. *The chronic kidney disease model: a general purpose model of disease progression and treatment*	General population	According to the authors, the model can accommodate treatment with ACE inhibitors, ARB, statin, management by a nephrologist, control of diabetes and hypertension, calcium and phosphorus management; CKD screening programme. However, only one hypothetical treatment is presented (20% relative reduction in vascular disease). It is unclear how the treatment pathway is implemented, given the many inter-relations between model states. Cardiovascular complications modelled include myocardial infarction, stroke and congestive heart failure	No CKD, CKD stage G1, CKD stage G2, CKD stage G3, CKD stage G4, CKD stage G5, kidney transplantation, haemodialysis	• Costs: no • Utilities: yes, estimates for each cardiovascular complication, dialysis and transplant	Estimates of all model parameters were derived from literature, based on experts' opinion or from an analysis of an external data set	Lifetime Markov Monte Carlo simulation with a monthly transition cycle. In each cycle, patient's CKD state and complications are determined. Transition probabilities between CKD stages and to cardiovascular conditions depend on patient's current CKD stage. In addition, at each stage, the patients could develop comorbid conditions (e.g. diabetes, hypertension or calcium/phosphorus abnormalities)	Yes: model outputs for myocardial infarction, mortality rates and GFR changes were compared with those reported in literature

continued

TABLE 8 Summary of identified cost-effectiveness models in CKD (*continued*)

Model identifier	Target population	Modelled interventions, cardiovascular end points and treatment pathways	Modelled CKD stages	Modelled costs and quality-of-life utilities	Data sources	Structure	Validation
Schlackow *et al.*,[36] 2017. *A policy model of cardiovascular disease in moderate-to-advanced chronic kidney disease*	Patients with CKD stage G3b or more advanced, including those with a kidney transplant or on dialysis	Lipid-lowering or other treatments directly affecting risk of cardiovascular end points (major atherosclerotic or vascular event). Incidence of cardiovascular events is assumed to be affected directly by the treatment, as well as indirectly as contemporaneous CVD history affects future cardiovascular events and CKD progression in the model	CKD stage G3b, CKD stage G4, CKD stage G5, kidney transplantation, dialysis	• Costs: yes, health-care costs for each state and for interventions' potential side effects • Utilities: yes, quality-of-life utilities for each disease state; quality-of-life decrements for interventions' potential side effects	Model parameters were derived from the individual patient-level data in the SHARP randomised control trial. External literature/data sets were used for non-vascular disease risks and statin adverse effects	Lifetime Markov cohort simulation with an annual transition cycle. In each cycle, a patient's CKD stage and cardiovascular complications were modelled. All transition probabilities were derived from parametric risk equations and depend on patient's baseline characteristics, and time-updated CKD state and CVD history	Yes: model-predicted rates of disease events were compared with those observed in the SHARP trial and three external cohorts. Predicted 5-year risks of major events were compared with observed rates in SHARP and those predicted by other models widely used in CVD or CKD

ARB, angiotensin II receptor blockers; NHANES, National Health and Nutrition Examination Survey; SHARP, Study of Heart and Renal Protection; USRDS, United States Renal Data System.

TABLE 9 Comparison of the included CKD models against the suitability criteria

Study/model	Suitability criteria			
	Does the target population include a separate category of patients with an eGFR of 60–90 ml/minute/1.73 m^2?	Are major cardiovascular events (e.g. myocardial infarction, stroke, heart failure) included in the model and do these allow implementing effects of treatments?	Were dialysis and renal transplantation modelled separately?	Was any model validation done?
Erickson *et al.*[32]	No	Yes, excluding heart failure	No	Yes
Go *et al.*[37]	No	Yes, excluding heart failure	Yes	Yes
Hoerger *et al.*[33,34]	No	No	No	Yes
Orlando *et al.*[35]	No	Yes, but unclear how	Yes	Yes
Schlackow *et al.*[36]	No	Yes, excluding heart failure	Yes	Yes

Appendix 13 Cost-effectiveness model in people with reduced kidney function

Schlackow *et al.*[38] https://doi.org/10.1371/journal.pmed.1003478

Appendix 14 Cost-effectiveness of monitoring kidney function in UK primary care

Introduction

The association between increasing kidney function impairment and increasing cardiovascular and other adverse events is well recognised.[97,98] Current guidelines for the management of CKD underline the need to monitor kidney function and reduce CVD risks accordingly.[11,42] In the UK, NICE recommends kidney function monitoring in people with, or at risk of, CKD using eGFR with the frequency of monitoring determined by the degree of kidney function impairment and the presence of proteinuria measured by the urinary ACR.[11] The evidence base for the recommended frequencies of GFR monitoring, however, is unclear. Current guidelines recommend that cardiovascular preventative treatments (i.e. statin, antihypertensive or antiplatelet) are considered for patients with reduced kidney function. For people with clinical CKD (i.e. meeting the CKD definition in the KDIGO guideline[42] adopted by NICE[11]) statin treatment is recommended, many of whom are also indicated for antihypertensive treatment and, if they have had a prior CVD diagnosis, for antiplatelet therapy. These therapies are also widely recommended for people with CVD.[11,99] Therefore, under current guidelines, monitoring eGFR among patients with clinical CKD or with a history of CVD is not expected to modify the indication for cardiovascular therapies.

The category of patients who could derive benefit from eGFR monitoring are those with mildly impaired kidney function (eGFR of 60–90 ml/minute/1.73 m^2), not yet with clinical CKD and without previous CVD, and this is the category of patients for whom we studied the cost-effectiveness of different frequencies of eGFR monitoring.

We used the CPRD CKD–CVD model, a long-term cost-effectiveness model of declining kidney function, and evolving CVD and mortality,[38] to assess the long-term health outcomes and health-care costs, under kidney function monitoring regimens of different frequency in UK primary care. The comparative cost-effectiveness of different regimens in categories of patients with reduced kidney function is also summarised.

Methods

The study was developed from the perspective of the UK health service and took a lifetime patient perspective. The health benefits were measured in incremental QALYs. We report incremental costs per QALY with future costs and QALYs discounted at 3.5% per year, as recommended in the NICE reference case.[100]

Study population

We assessed the value of eGFR monitoring of different frequency among people with evidence of declining kidney function (eGFR < 90 ml/minute/1.73 m^2) in UK primary care.[101] From the overall open cohort of patients with eGFR 60–90 ml/minute/1.73 m^2 [38] and without a history of CVD in CPRD, we randomly sampled 5000 men and 5000 women while maintaining the age distribution in each group.

Kidney function monitoring regimens assessed

We assessed the following frequencies of eGFR monitoring: 'no monitoring', and monitoring every 1, 2, 3, 4 and 5 years. In discussions with members of the Programme Management Group and stakeholders, it was agreed that the key objective of eGFR monitoring in primary care is to guide treatments to reduce cardiovascular risk among people with reduced kidney function. The latest NICE clinical guideline for management of adults with CKD[11] and adults with eGFR 60–90 ml/minute/1.73 m^2 but no CKD[99] was used to derive a schematic of the use of the three classes of guideline-indicated cardiovascular prevention pharmacotherapies (i.e. statins, antihypertensive and antiplatelet) to implement in the CPRD CKD–CVD model (*Table 10*). We used the QRISK3 risk score to annually calculate the CVD risk among people without previous CVD.[102] Atorvastatin 20 mg daily, the statin treatment recommended for people without a history of CVD but with clinical CKD, and atorvastatin 80 mg/daily, the statin treatment recommended for all other patients indicated for statin treatment, were used. We used ramipril 10 mg capsule daily, the most widely used antihypertensive in England,[103] to simulate the cost of antihypertensive treatment (relative risk reductions across ACE inhibitors were used), and aspirin 75 mg daily for the use of antiplatelet treatment. The treatment effects of these three classes of treatments were informed from recent meta-analyses of randomised evidence for the therapies[39–41] (*Table 11*).

TABLE 10 Pharmacotherapies to manage cardiovascular risk implemented in eGFR monitoring scenarios

Pharmacotherapy	Without history of CVD	With history of CVD
Statin therapy	Atorvastatin 20 mg per day for people: • with a ≥ 10% 10-year QRISK3 CVD risk • who have CKD[a] • aged ≥ 85 years • who have type 1 diabetes	Atorvastatin 80 mg/day

Antihypertensive therapy	Antihypertensive treatment (ramipril 10 mg per day) for people:
	• who have CKD and one (or more) of
	  ○ diabetes and microalbuminuria[b] or macroalbuminuria[c]
	  ○ macroalbuminuria
	• who have stage 1 hypertension[d] and one (or more) of the following
	  ○ CVD
	  ○ CKD
	  ○ diabetes
	  ○ ≥ 10% QRISK3 risk
	• who have stage 2 hypertension[e] or higher	

Antiplatelet therapy	None	Aspirin 75 mg per day

a CKD is defined as either having an eGFR of < 60 ml/minute/1.73m^2; or having an eGFR of 60–90 ml/minute/1.73m^2 plus microalbuminuria/macroalbuminuria or a further marker of renal damage.
b Microalbuminuria is defined as an albumin–to–creatinine ratio of 3–30 mg/mmol.
c Macroalbuminuria is defined as an albumin–to–creatinine ratio of > 30 mg/mmol.
d Stage 1 hypertension is defined as systolic blood pressure ≥ 140 to ≤ 159 mmHg or diastolic blood pressure ≥ 90 to ≤ 99 mmHg at entry.
e Stage 2 hypertension or higher is defined as systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg at entry.

TABLE 11 Relative risk reduction with treatments to prevent CVD

Treatment and dose (mg per day)	CKD stage, rate ratio (95% CI)					
	G2	G3a	G3b	G4	G5	Dialysis
Atorvastatin, 20 mg[a,b]						
Vascular death	0.78 (0.73 to 0.85)	0.88 (0.80 to 0.97)	0.90 (0.79 to 1.02)	0.81 (0.69 to 0.95)	0.82 (0.70 to 0.96)	1.00 (0.87 to 1.15)
MI	0.65 (0.60 to 0.69)	0.64 (0.57 to 0.73)	0.74 (0.61 to 0.91)	0.82 (0.62 to 1.09)	0.83 (0.63 to 1.09)	0.85 (0.66 to 1.10)
Stroke	0.77 (0.70 to 0.85)	0.75 (0.65 to 0.87)	0.89 (0.72 to 1.10)	0.80 (0.62 to 1.03)	0.81 (0.63 to 1.09)	1.11 (0.86 to 1.42)
Atorvastatin, 80 mg[a,b]						
Vascular death	0.75 (0.68 to 0.82)	0.86 (0.76 to 0.97)	0.88 (0.76 to 0.97)	0.77 (0.63 to 0.94)	0.78 (0.65 to 0.95)	1.00 (0.84 to 1.19)
MI	0.59 (0.54 to 0.64)	0.58 (0.50 to 0.68)	0.70 (0.55 to 0.89)	0.79 (0.56 to 1.11)	0.80 (0.57 to 1.11)	0.82 (0.60 to 1.13)
Stroke	0.73 (0.65 to 0.83)	0.71 (0.59 to 0.85)	0.87 (0.67 to 1.12)	0.76 (0.56 to 1.04)	0.77 (0.57 to 1.04)	1.13 (0.84 to 1.53)
ACEI[c,d]						
Vascular death	0.87 (0.78 to 0.98)	0.80 (0.69 to 0.93)	0.80 (0.69 to 0.93)	0.80 (0.69 to 0.93)	0.80 (0.69 to 0.93)	0.80 (0.69 to 0.93)
MI	0.79 (0.75 to 0.87)	0.81 (0.71 to 0.93)	0.81 (0.71 to 0.93)	0.81 (0.71 to 0.93)	0.81 (0.71 to 0.93)	0.81 (0.71 to 0.93)
Stroke	0.85 (0.71 to 1.03)	0.81 (0.68 to 0.96)	0.81 (0.68 to 0.96)	0.81 (0.68 to 0.96)	0.81 (0.68 to 0.96)	0.81 (0.68 to 0.96)
Heart failure hospitalisation	0.90 (0.74 to 1.09)	0.75 (0.63 to 0.91)	0.75 (0.63 to 0.91)	0.75 (0.63 to 0.91)	0.75 (0.63 to 0.91)	0.75 (0.63 to 0.91)
Aspirin 75 mg[d,e]						
Vascular death	0.87 (0.65 to 1.15)	0.87 (0.65 to 1.15)	0.87 (0.65 to 1.15)	0.87 (0.65 to 1.15)	0.87 (0.65 to 1.15)	0.87 (0.65 to 1.15)
MI	0.68 (0.46 to 0.99)	0.68 (0.46 to 0.99)	0.68 (0.46 to 0.99)	0.68 (0.46 to 0.99)	0.68 (0.46 to 0.99)	0.68 (0.46 to 0.99)
Stroke	1.00 (0.58 to 1.72)	1.00 (0.58 to 1.72)	1.00 (0.58 to 1.72)	1.00 (0.58 to 1.72)	1.00 (0.58 to 1.72)	1.00 (0.58 to 1.72)

ACEI, angiotensin-converting-enzyme inhibitor; MI, myocardial infarction.
a Ballantyne *et al.*[104] (table II: % change from baseline for LDL-cholesterol).
b Herrington *et al.*[41]
c Ninomiya *et al.*[39]
d Patients on transplant assumed to have the same treatment effects as those in G3a in lieu of other information.
e Palmer *et al.*[40]
For each statin dose considered, the effects on vascular end points were expressed as relative risk reduction for each eGFR category separately. First, the absolute reduction in LDL cholesterol was sourced for each eGFR category using information on the proportional reduction in LDL cholesterol[104] and LDL cholesterol at baseline by renal function category (see *Table 14*). These absolute reductions were combined with the rate ratios for vascular events per 1 mmol reduction in LDL cholesterol as reported by Herrington *et al.*[41]

The impact of kidney function monitoring on an individual's health is driven by the actions taken (e.g. treatments initiated) to improve the patient's health using the acquired new information about the patient's kidney function from monitoring. For example, statin therapy is not recommended for patients with mildly reduced kidney function (eGFR > 60 ml/minutes/1.73m^2) if they are otherwise at low cardiovascular risk (i.e. without albuminuria or other cardiovascular risk factors), but is recommended for the same patients if their kidney function declines below 60 ml/minute/1.73 m^2.[11,99] We assessed the value of different frequencies of GFR monitoring among people with reduced kidney function assuming that the NICE clinical guidelines for the management of CKD[11] and cardiovascular risk[99] were fully implemented. In our assessment, all patients indicated (because of a new cardiovascular event or increased cardiovascular risk) or, in the course of GFR monitoring (i.e. decline of kidney function), becoming indicated for particular cardiovascular therapies (i.e. statin, antihypertensive or antiplatelet) and receiving the respective guideline-indicated therapies. Statins are associated with small increases in the risk of incident diabetes, myopathy and rhabdomyolysis.[105] Declining kidney function and use of ACE inhibitors are both associated with increased risk of acute kidney injury.[106] Increased rates of these and associated health-care costs and quality-of-life effects were implemented in the monitoring scenarios simulated (*Table 12*).

TABLE 12 Adverse events associated with cardiovascular preventative therapies

Adverse event	Incidence per 100,000 treated (per year)	Quality-of-life decrement (per case)	Health-care cost (per case) (£, 2018)
Statin (excess risks related to treatment)[a]			
Myopathy	11	0.0014[b]	38.95[b]
Rhabdomyolysis	3.4	2.67%[b] 10% risk of death	3827[c]
Diabetes	98 (atorvastatin 20 mg/day)[d]		
	299 (atorvastatin 80 mg/day)[e,f]		
Acute kidney injury (not on ACEI)[f] ***risk due to CKD***			
G3a	5.5	0.07825	1995[g]
G3b	17.9	0.07825	1995
G4	46.1	0.07825	1995
Acute kidney injury (on ACEI)[f] ***excess risk due to ACEI***			
G3a	0.9	0.07825	1995
G3b	3.2	0.07825	1995
G4	8.3	0.07825	1995

ACEI, angiotensin-converting-enzyme inhibitor; GBP, Great British pounds; USD, US dollar.

a Law and Rudnicka.[105]

b Pletcher *et al.*[107] It is assumed that a case of rhabdomyolysis has a utility decrement of 50% for the 7.5 days in hospital and then a decrement of 20% for the 30 days after hospitalisation. Myopathy quality of life decreases by 0.017 over 30 days. Myopathy cost includes three creatinine-kinase tests delivered by a nurse.

c The cost of hospitalisation for rhabdomyolysis is based on NHS reference costs[108] for Healthcare Resource Group (HRG) HD21D Soft Tissue Disorders with CC Score 12+; non-elective long stay.

d Sattar *et al.*[109]

e Preiss *et al.*[110]

f Mansfield *et al.*[106] Note that (1) excess rates will be modelled (over and above the rates for people without CKD – classified by the paper as eGFR ≥ 60 ml/minute/1.73 m^2); (2) those 'not exposed' to ACE inhibitors will have the same risk as an individual not on antihypertensives; and (3) if a patient has an acute kidney injury they will not stop their treatment.

g Average NHS reference costs[108] for acute kidney injury.

The analytical approach

The CPRD CKD–CVD model was developed using a large, open cohort of patients with reduced kidney function (eGFR < 90 ml/minute/1.73 m^2). The model was derived from the UK CPRD database of routine health-care data from 388 general practices in England with the CPRD data linked to UK Hospital Episode Statistics mortality data from the Office for National Statistics and the Townsend multiple deprivation quintile. It was used to simulate the long-term health outcomes and health-care costs of patients under different monitoring regimens. The model, described in detail in Schlackow *et al.*,[38] uses kidney function decline and cardiovascular risk estimates, derived from the CPRD cohort and quality-of-life[36,99,111] and UK-specific costs[112,113] for each model state informed from published sources.

The underlying trajectories of eGFR were modelled using the statistical models for the deterioration of kidney function, outlined in Oke *et al.*[26] The calculated 'observed' eGFR categories from these models were used, rather than the calculated 'true' eGFR categories, to reflect the use of observed eGFR in the modelling of CVD risks, in the randomised trials for cardiovascular treatments, and during monitoring of eGFR in primary care where observed measure of kidney function informs disease management decisions.

The impact of eGFR monitoring was implemented in the models via updating of the eGFR category in the annual period in which the kidney function was 'measured' given the particular monitoring frequency. This updated, observed eGFR category informs the review of treatments. For example, in the scenarios of 'no monitoring', patients' eGFR categories remain fixed at their entry into the model levels throughout the duration of the simulation for the purpose of eGFR-driven treatment initiation, while in the scenarios with annual monitoring, patients' eGFR category is updated annually for the same purpose. Independently of eGFR monitoring frequency, however, patients' underlying kidney function is updated annually in the model to drive projection of cardiovascular risk and survival.

Cost of estimated glomerular filtration rate monitoring and related cardiovascular therapies

Each eGFR monitoring cycle in simulations involves a creatinine test and a nurse visit (*Table 13*). The costs of atorvastatin of 20 and 80 mg per day, ramipril of 10 mg per day and aspirin of 75 mg per day were informed by the NHS drug tariff.[114] NICE guidelines informed the resources for monitoring statin treatment (i.e. an annual medication review with a nurse including cholesterol test) and antihypertensive (e.g. annual clinic blood pressure measurement with nurse appointment).[11,99,115] It was assumed that, if indicated, a single nurse appointment in a year (replaced by a GP appointment once every 5 years) would be sufficient to monitor CKD progression and all three classes of cardiovascular medications.

Results

The baseline characteristics of the 10,000 sampled cohort of patients with reduced kidney function, used to simulate results of eGFR monitoring strategies, are presented in *Table 14*, overall and by age at start of monitoring.

The results from our scenarios of frequency of eGFR monitoring regimens in people with reduced kidney function, without a history of CVD, followed by guideline-recommended cardiovascular pharmacotherapies, indicate that, on average, across this target population and eGFR levels, a monitoring regimen every 4 years may be cost-effective at a threshold of £20,000 per QALY (*Table 15*). However, the patient's age at the start of monitoring has an important effect on the cost-effective frequency of monitoring. At a threshold of £20,000K per QALY, the cost-effective frequencies of eGFR monitoring were every 3 years among people aged < 60 years, every 4 years among people aged 60–69 years, and monitoring

TABLE 13 Cost involved in monitoring eGFR and CVD pharmacotherapies

Category of resources	Costs (£, 2018/19)	Source and further notes
Health-care resources involved in monitoring eGFR		
Creatinine test; total cholesterol test	1.10	*2018/2019 National Cost Collection Data*[116] for a clinical biochemistry test
Appointment with a nurse	11.88	*Unit Costs of Health and Social Care 2019*;[117] cost of a 20-minute nurse (band 6) appointment
Pharmacotherapies		
Statin (per 28 days)	0.81 (atorvastatin 20 mg/day)	*NHS Electronic Drug Tariff*[114]
	1.65 (atorvastatin 80 mg/day)	
Antihypertensive (per 28 days)	1.08 (ramipril 10 mg)	*NHS Electronic Drug Tariff*.[114] Note that the *Prescription Cost Analysis England 2017/2018*[103] identifies ramipril 10-mg capsules as the most commonly used ACEI and, therefore, ramipril 10-mg capsules have been used to cost ACEI in the scenarios
Antiplatelet (per 28 days)	0.71 (aspirin 75 mg)	*NHS Electronic Drug Tariff*[114]
Extra annual monitoring with or without pharmacotherapies		
Statin	12.98 or 34.10 (every 5 years)	*Unit Costs of Health and Social Care 2019*[117] and *2018/2019 National Cost Collection Data*;[116] an appointment with a nurse, or (every 5 years) a GP, plus a non-HDL cholesterol test
Antihypertensive	11.88 or 33.00 (every 5 years)	*Unit Costs of Health and Social Care 2019*;[117] an appointment with a nurse (including blood pressure test), or (every 5 years) a GP; only if statin is not used concomitantly (otherwise in same visit with statin annual check)
Antiplatelet/anticoagulant	–	Administered at the same time with statin or antihypertensive; no extra monitoring costs
CKD progression	–	Administered at the same time with statin, as all patients with CKD need to be prescribed statins

ACEI, angiotensin-converting-enzyme inhibitor; HDL, high-density lipoprotein.

was not cost-effective among people aged ≥ 70 years. Compared with no eGFR monitoring strategies, these regimens of monitoring would produce 0.2732 extra QALYs per person monitored among those aged < 60 years and 0.0524 extra QALYs among those aged 60–69 years. The components of long-term costs with monitoring strategies of different frequencies (*Table 16*) indicate that the direct eGFR monitoring and cardiovascular treatment costs contribute similarly to the excess costs related to different strategies.

Discussion

In the present study, the cost-effectiveness of different intervals of eGFR monitoring among people with eGFR 60–90 ml/minute/1.73 m^2 but without a history of CVD, and without albuminuria, were evaluated. Among these patients, the cost-effective interval of monitoring ranged from every 3 years among patients aged < 60 years to no monitoring among those aged ≥ 70 years and produced from 0.27 to 0.05 extra QALYs per person monitored across the age categories < 60 years and 60–69 years. There was a gradual decrease in the indicated cost-effective frequency of monitoring with increasing age and monitoring was not cost-effective above the age of 70 years.

TABLE 14 Baseline characteristics of patients with eGFR 60–90 ml/minute/1.73 m^2 without a history of CVD in CPRD used to simulate eGFR monitoring scenarios

Characteristic	18–59 years	60–69 years	70–79 years	≥ 80 years	All with eGFR 60–90 ml/minute/1.73 m^2
n	5404	2645	1500	451	10,000
Age (years)	50 (8)	65 (3)	75 (3)	85 (4)	59 (13)
Male	2581 (48%)	1450 (55%)	771 (51%)	198 (44%)	5000 (50%)
Never smoked	3002 (56%)	1329 (50%)	793 (53%)	267 (59%)	5391 (54%)
Current smoker	1178 (22%)	450 (17%)	204 (14%)	45 (10%)	1877 (19%)
Previous smoker	1224 (23%)	866 (33%)	503 (34%)	139 (31%)	2732 (27%)
Body mass index	28 (6)	28 (7)	27 (5)	25 (4)	28 (6)
Systolic blood pressure	132 (17)	139 (17)	142 (18)	143 (18)	136 (18)
Diastolic blood pressure	81 (10)	81 (10)	79 (10)	77 (10)	80 (10)
HDL cholesterol	1.4 (0.4)	1.5 (0.4)	1.5 (0.4)	1.6 (0.5)	1.5 (0.4)
LDL cholesterol	3.3 (1.0)	3.3 (1.0)	3.1 (1.0)	3.1 (1.0)	3.3 (1)
Total cholesterol	5.4 (1.1)	5.3 (1.1)	5.2 (1.1)	5.4 (1.1)	5.4 (1.1)
Hypertension (Read code)	1362 (25%)	1083 (41%)	697 (46%)	191 (42%)	3333 (33%)
Rheumatoid arthritis	75 (1%)	37 (1%)	31 (2%)	4 (1%)	147 (1%)
Family history of coronary heart disease	1110 (21%)	470 (18%)	225 (15%)	29 (6%)	1834 (18%)
Diabetes, type 1	24 (0%)	0 (0%)	1 (0%)	0 (0%)	25 (0%)
Diabetes, type 2	392 (7%)	319 (12%)	195 (13%)	36 (8%)	942 (9%)
Cancer	176 (3%)	217 (8%)	186 (12%)	68 (15%)	647 (6%)
Albuminuria, not measured	3249 (60%)	1477 (56%)	790 (53%)	237 (53%)	5753 (58%)
Albuminuria, measured and normal	2089 (39%)	1114 (42%)	684 (46%)	205 (45%)	4092 (41%)
Indicated statins at baseline[a]	1362 (25%)	2162 (82%)	1498 (100%)	451 (100%)	5473 (55%)
Indicated antihypertensives at baseline[a]	1072 (20%)	1254 (47%)	873 (58%)	281 (62%)	3480 (35%)
Stage 1 hypertension[b] and no diabetes (i.e. would be indicated antihypertensives if eGFR declines to < 60 ml/minute/1.73 m^2)	941 (17%)	141 (5%)	0 (0%)	0 (0%)	1082 (11%)

HDL, high-density lipoprotein.
a As per criteria in *Table 10*.
b Systolic blood pressure between ≥ 140 and ≤ 159 ≤ 99 mmHg or diastolic blood pressure between ≥ 90 and ≤ 99 mmHg.
Values presented are mean (SD) or *n* (%).

Current NICE guidance suggests that less than annual monitoring of kidney function is sufficient among patients with eGFR 60–90 ml/minute/1.73 m^2 but does not recommend a particular frequency of monitoring.[11] Although our results are concordant with this guidance, they go further to suggest that the optimal interval of monitoring would depend on the patient's age, with older patients unlikely to benefit cost-effectively from eGFR monitoring.

In the present study, we focused on people with only mildly reduced kidney function and without a history of CVD. This was motivated by the observation that people with eGFR< 60 ml/minute/1.73 m^2 or a history of CVD are already indicated for the cardiovascular prevention therapies used with monitoring.[11]

TABLE 15 Long-term effects and cost-effectiveness of monitoring individuals with eGFR 60–90 ml/minute/1.73 m^2 without a history of CVD

Patient category	Total cost (£)	Life-years	QALYs	Incremental cost (vs. next less frequent monitoring)	Incremental QALYs (vs. next less frequent monitoring)	Incremental cost per QALY[a] (vs. next less frequent monitoring)
All						
No monitoring	24,430 (22,160 to 26,758)	29.2712 (28.8275 to 29.6388)	21.858 (21.2676 to 22.3747)	–	–	–
5-yearly monitoring	24,705 (22,399 to 27,045)	29.3548 (28.9076 to 29.7223)	22.0147 (21.4174 to 22.5395)	274 (211 to 345)	0.1567 (0.1278 to 0.1823)	3173 (2526 to 4221)
4-yearly monitoring	24,726 (22,420 to 27,066)	29.3559 (28.9087 to 29.7236)	22.0172 (21.4196 to 22.5423)	22 (21 to 22)	0.0025 (0.0021 to 0.0028)	12,185 (10,507 to 14,298)
3-yearly monitoring	24,765 (22,459 to 27,106)	29.3571 (28.9098 to 29.725)	22.0199 (21.4218 to 22.5452)	39 (39 to 40)	0.0026 (0.0023 to 0.003)	21,333 (18,476 to 25,007)
2-yearly monitoring	24,836 (22,528 to 27,177)	29.3581 (28.9109 to 29.7261)	22.0222 (21.4239 to 22.5476)	70 (69 to 71)	0.0024 (0.002 to 0.0027)	41,226 (35,771 to 48,505)
Annual monitoring	25,033 (22,725 to 27,375)	29.3592 (28.9119 to 29.7269)	22.0246 (21.4259 to 22.5499)	197 (194 to 200)	0.0024 (0.0021 to 0.0028)	110,451 (95,716 to 129,435)
Age < 60 years						
No monitoring	31,400 (28,327 to 34,559)	38.4411 (37.8221 to 38.9387)	28.9296 (28.1554 to 29.6081)	–	–	–
5-yearly monitoring	31,821 (28,701 to 34,955)	38.5778 (37.969 to 39.0887)	29.1945 (28.406 to 29.879)	422 (314 to 543)	0.2649 (0.2154 to 0.3082)	2865 (2240 to 3860)
4-yearly monitoring	31,851 (28,730 to 34,984)	38.5795 (37.9705 to 39.0903)	29.1985 (28.41 to 29.8828)	29 (28 to 30)	0.004 (0.0034 to 0.0046)	10,188 (8761 to 12,039)
3-yearly monitoring	31,904 (28,783 to 35,038)	38.5813 (37.9724 to 39.0921)	29.2028 (28.4143 to 29.8869)	54 (53 to 55)	0.0043 (0.0037 to 0.0049)	17,786 (15,405 to 20,904)
2-yearly monitoring	31,999 (28,876 to 35,132)	38.5829 (37.9743 to 39.0936)	29.2066 (28.4181 to 29.8906)	94 (92 to 96)	0.0038 (0.0033 to 0.0044)	33,726 (29,292 to 39,630)
Annual monitoring	32,260 (29,133 to 35,395)	38.5845 (37.9761 to 39.0952)	29.2105 (28.422 to 29.8943)	261 (257 to 265)	0.0039 (0.0033 to 0.0045)	88,473 (76,709 to 103,846)
Age 60–69 years						
No monitoring	19,572 (17,845 to 21,294)	22.5154 (22.1987 to 22.7779)	16.5549 (16.0866 to 16.9694)	–	–	–
5-yearly monitoring	19,717 (18,000 to 21,430)	22.5521 (22.2358 to 22.8127)	16.606 (16.1303 to 17.0198)	145 (125 to 167)	0.0512 (0.0421 to 0.0591)	4256 (3540 to 5418)
4-yearly monitoring	19,732 (18,016 to 21,445)	22.5529 (22.2365 to 22.8134)	16.6073 (16.1315 to 17.021)	15 (15 to 16)	0.0012 (0.0011 to 0.0014)	14,751 (12,748 to 17,284)
3-yearly monitoring	19,761 (18,045 to 21,473)	22.5536 (22.2372 to 22.8141)	16.6085 (16.1327 to 17.0221)	29 (28 to 29)	0.0012 (0.001 to 0.0014)	27,957 (24,079 to 32,892)
2-yearly monitoring	19,813 (18,097 to 21,525)	22.5543 (22.2378 to 22.8147)	16.6096 (16.1338 to 17.0232)	52 (51 to 53)	0.0011 (0.001 to 0.0013)	53,329 (45,887 to 62,706)
Annual monitoring	19,962 (18,246 to 21,675)	22.5549 (22.2384 to 22.8153)	16.6108 (16.1349 to 17.0243)	150 (148 to 151)	0.0012 (0.001 to 0.0013)	146,044 (125,294 to 172,860)

Patient category	Total cost (£)	Life-years	QALYs	Incremental cost (vs. next less frequent monitoring)	Incremental QALYs (vs. next less frequent monitoring)	Incremental cost per QALY[a] (vs. next less frequent monitoring)
Age 70–79 years						
No monitoring	12,959 (11,826 to 14,009)	14.5129 (14.3403 to 14.6449)	10.5539 (10.2507 to 10.8139)	–	–	–
5-yearly monitoring	13,003 (11,870 to 14,054)	14.5131 (14.3406 to 14.6451)	10.5541 (10.2509 to 10.8142)	45 (44 to 45)	0.0002 (0.0002 to 0.0003)	273,239 (231,518 to 337,069)
4-yearly monitoring	13,013 (11,880 to 14,063)	14.5131 (14.3406 to 14.6451)	10.5542 (10.2509 to 10.8142)	9 (9 to 9)	< 0.0001	694,078 (590,086 to 820,561)
3-yearly monitoring	13,028 (11,895 to 14,079)	14.5131 (14.3406 to 14.6451)	10.5542 (10.2509 to 10.8142)	16 (16 to 16)	< 0.0001	1,141,711 (969,606 to 1,358,290)
2-yearly monitoring	13,060 (11,926 to 14,110)	14.5131 (14.3406 to 14.6452)	10.5542 (10.251 to 10.8142)	31 (31 to 32)	< 0.0001	2,240,790 (1,902,092 to 2,693,706)
Annual monitoring	13,153 (12,020 to 14,204)	14.5131 (14.3406 to 14.6452)	10.5542 (10.251 to 10.8142)	94 (93 to 95)	< 0.0001	11,647,270 (9,879,952 to 14,013,001)
Age ≥ 80 years						
No monitoring	7572 (6945 to 8176)	8.1008 (8.0015 to 8.1775)	5.8227 (5.6568 to 5.9727)	–	–	–
5-yearly monitoring	7600 (6973 to 8204)	8.1008 (8.0015 to 8.1775)	5.8227 (5.6568 to 5.9727)	28 (27 to 28)	0	N/A
4-yearly monitoring	7605 (6978 to 8209)	8.1008 (8.0015 to 8.1775)	5.8227 (5.6568 to 5.9727)	5 (5 to 5)	0	N/A
3-yearly monitoring	7614 (6987 to 8218)	8.1008 (8.0015 to 8.1775)	5.8227 (5.6568 to 5.9727)	9 (8 to 9)	0	N/A
2-yearly monitoring	7631 (7004 to 8235)	8.1008 (8.0015 to 8.1775)	5.8227 (5.6568 to 5.9727)	17 (17 to 18)	0	N/A
Annual monitoring	7683 (7056 to 8287)	8.1008 (8.0015 to 8.1775)	5.8227 (5.6568 to 5.9727)	52 (51 to 52)	0	N/A

N/A, not applicable.
a With incremental costs and QALYs discounted.

TABLE 16 Long-term costs in scenarios of eGFR monitoring in individuals with eGFR 60–90 ml/minute/1.73 m^2 without a history of CVD

Patient category	Total cost (£)	eGFR monitoring cost (£)	Cost of CVD treatments, monitoring and adverse effects (£)	Hospital care costs (£)
All				
No monitoring	24,430 (22,135 to 26,760)	–	807 (787 to 824)	23,623 (21,344 to 25,958)
5-yearly monitoring	24,705 (22,396 to 27,053)	83 (81 to 83)	1193 (1170 to 1213)	23,429 (21,123 to 25,775)
4-yearly monitoring	24,726 (22,417 to 27,075)	102 (100 to 103)	1197 (1174 to 1217)	23,427 (21,120 to 25,773)
3-yearly monitoring	24,765 (22,455 to 27,114)	133 (131 to 135)	1207 (1184 to 1227)	23,425 (21,117 to 25,771)
2-yearly monitoring	24,836 (22,523 to 27,183)	197 (194 to 199)	1216 (1193 to 1236)	23,423 (21,114 to 25,769)
Annual monitoring	25,033 (22,716 to 27,380)	387 (381 to 391)	1225 (1202 to 1245)	23,421 (21,112 to 25,766)
Age < 60 years				
No monitoring	31,400 (28,239 to 34,570)	–	764 (737 to 787)	30,636 (27,511 to 33,802)
5-yearly monitoring	31,821 (28,650 to 34,975)	106 (105 to 108)	1413 (1381 to 1441)	30,302 (27,160 to 33,433)
4-yearly monitoring	31,851 (28,678 to 35,004)	131 (129 to 133)	1420 (1388 to 1449)	30,299 (27,157 to 33,429)
3-yearly monitoring	31,904 (28,730 to 35,057)	173 (170 to 175)	1436 (1404 to 1464)	30,295 (27,153 to 33,424)
2-yearly monitoring	31,999 (28,821 to 35,151)	256 (252 to 259)	1450 (1418 to 1479)	30,292 (27,150 to 33,419)
Annual monitoring	32,260 (29,076 to 35,412)	506 (498 to 512)	1465 (1433 to 1493)	30,289 (27,146 to 33,415)
Age 60–69 years				
No monitoring	19,572 (17,837 to 21,294)	–	980 (964 to 995)	18,591 (16,854 to 20,321)
5-yearly monitoring	19,717 (17,991 to 21,442)	65 (64 to 66)	1113 (1095 to 1128)	18,539 (16,811 to 20,254)
4-yearly monitoring	19,732 (18,006 to 21,458)	79 (78 to 80)	1115 (1097 to 1129)	18,538 (16,810 to 20,254)
3-yearly monitoring	19,761 (18,035 to 21,487)	104 (102 to 105)	1120 (1102 to 1135)	18,537 (16,809 to 20,253)
2-yearly monitoring	19,813 (18,087 to 21,539)	152 (150 to 154)	1124 (1106 to 1139)	18,536 (16,808 to 20,252)
Annual monitoring	19,962 (18,237 to 21,689)	298 (294 to 302)	1128 (1111 to 1143)	18,535 (16,808 to 20,252)

Patient category	Total cost (£)	eGFR monitoring cost (£)	Cost of CVD treatments, monitoring and adverse effects (£)	Hospital care costs (£)
Age 70–79 years				
No monitoring	12,959 (11,813 to 14,009)	–	766 (756 to 774)	12,193 (11,048 to 13,241)
5-yearly monitoring	13,003 (11,857 to 14,054)	44 (44 to 44)	766 (757 to 774)	12,193 (11,048 to 13,241)
4-yearly monitoring	13,013 (11,866 to 14,063)	53 (53 to 54)	766 (757 to 774)	12,193 (11,048 to 13,241)
3-yearly monitoring	13,028 (11,882 to 14,079)	69 (68 to 70)	767 (757 to 774)	12,193 (11,048 to 13,241)
2-yearly monitoring	13,060 (11,913 to 14,110)	100 (99 to 101)	767 (757 to 774)	12,193 (11,048 to 13,241)
Annual monitoring	13,153 (12,007 to 14,204)	194 (192 to 196)	767 (757 to 774)	12,193 (11,048 to 13,241)
Age ≥ 80 years				
No monitoring	7572 (6942 to 8168)	–	444 (439 to 448)	7128 (6498 to 7723)
5-yearly monitoring	7600 (6970 to 8196)	28 (27 to 28)	444 (439 to 448)	7128 (6498 to 7723)
4-yearly monitoring	7605 (6975 to 8201)	33 (33 to 33)	444 (439 to 448)	7128 (6498 to 7723)
3-yearly monitoring	7614 (6984 to 8210)	41 (41 to 42)	444 (439 to 448)	7128 (6498 to 7723)
2-yearly monitoring	7631 (7001 to 8227)	59 (58 to 59)	444 (439 to 448)	7128 (6498 to 7723)
Annual monitoring	7683 (7053 to 8279)	111 (110 to 112)	444 (439 to 448)	7128 (6498 to 7723)

Monitoring eGFR among these patients for the purpose of initiating cardiovascular treatments, therefore, is unlikely to bring any further benefits under the assumption of full uptake and persistence with the indicated statin, antihypertensive and antiplatelet treatments.

In the present study, the effect of monitoring for albuminuria was not investigated because of a lack of sufficient ACR test data in primary care to allow models of trajectories of ACR to be developed. Annual screening for albuminuria, however, has been previously reported to be cost-effective in people with a history of diabetes.[7] We also did not model effects of lipid-lowering and glycaemic control interventions on CKD progression as no reliable evidence was identified to suggest that these treatments modified progression through CKD stages. Nevertheless, treatments that protect renal function have the potential to substantially improve the cost-effectiveness of CKD monitoring in primary care.

In the cost-effectiveness study, the observed eGFR during monitoring is used to inform treatment decisions during monitoring, and probabilities of misclassification due to test variability are explicitly modelled as recommended in economic evaluations of frequency of disease monitoring to penalise inappropriate actions because of this misclassification. In the context of the present study, however, there are no clear penalties for misclassification as the cardiovascular treatments used will be reducing cardiovascular risk even if misclassification of eGFR category has occurred (and the scenarios already include the safety issues with these medications). Furthermore, CVD risks in the present study, as well as treatment effectiveness of cardiovascular therapies in the randomised studies, were evaluated using observed measures of kidney function in the respective patients under rates of misclassification that were likely to be similar. Nevertheless, future studies could investigate the net effects of monitoring under an assumption for further dis-benefit from 'earlier' initiation of cardiovascular therapies.

A large, UK primary care data set and a detailed individual patient data-driven cost-effectiveness model informed the present analysis of frequency of eGFR monitoring in primary care. However, a number of potential limitations need to be acknowledged. First, we did not explicitly include screening for eGFR < 90 ml/minute/1.73 m^2 in our model, opting instead to study kidney function monitoring once patients were observed to have eGFR < 90 ml/minute/1.73 m^2. Although the vast majority of such patients in CPRD did not have a corresponding kidney function diagnosis code, their identification with automatic review of electronic records in primary care is likely to be straightforward. Second, although all patients in our target patient cohort did not have evidence of albuminuria at baseline (thus defined as without clinical CKD), we did not model their albuminuria status over time, nor did we investigate the effects of ACR monitoring as we did not have data on which to base such analyses. Similarly, blood pressure changes over time have also not been modelled. Future model development including modelling time trajectories of ACR and blood pressure in this population will be informative. Third, the present analyses focused exclusively on monitoring eGFR at earlier stages of kidney function decline to optimise cardiovascular risk reduction. Monitoring kidney function to guide early identification of people requiring dialysis/transplant or other interventions (e.g. vaccinations recommended at different CKD stages) was beyond the scope of this work. Finally, the present analyses are importantly based on the available patient data in routine primary care records. These data are influenced by indication-based measurement of disease and other clinical parameters (e.g. blood pressure is measured more often among people with higher blood pressure) with missing data probably not missing at random. Such data issues might have transcended in the disease model and, therefore, further validation of the model in different cohorts are required to confirm its validity.

In conclusion, the present analyses indicate that eGFR monitoring is indicated among people with mildly reduced kidney function and without CVD history up to the age of 70 years. In such patients, the optimal frequency of monitoring depends on the patient's age with patients aged < 60 years indicated for eGFR monitoring every 3 years, whereas those aged between 60 and 69 years are indicated for eGFR monitoring every 4 years. Monitoring eGFR among people aged ≥ 70 years, without CVD history and with only mildly reduced kidney function is not indicated.

Appendix 15 B-type natriuretic peptide-guided treatment for heart failure

McLellan *et al.*[67] https://doi.org/10.1002/14651858.CD008966.pub2

Appendix 16 Natriuretic peptide-guided treatment for heart failure: a systematic review and meta-analysis

McLellan *et al.*[68] https://doi.org/10.1136/bmjebm-2019-111208

Appendix 17 Remote monitoring, telemonitoring and structured telephone support to monitor heart failure: systematic review and meta-analysis

This project was conducted by Julie McLellan, Nicola Pidduck, Clare J Taylor, Kathryn S Taylor and Rafael Perera.

Introduction

Description of the condition

Heart failure is a condition in which the heart is unable to pump enough blood to supply sufficient oxygen to the rest of the body, leading to breathlessness, fatigue and oedema.[118] In the UK, an estimated 920,000 people have heart failure. Incidence increases with age and is highest in adults aged > 75 years. With an ageing population and improved survival of patients with heart disease, it is predicted that there will be an increasing prevalence of heart failure in the future.[119]

The goals of treatment in patients with established heart failure are to relieve symptoms, prevent hospital admission and, when possible, improve survival.[13,120] A range of drugs, in addition to devices and rehabilitation, have been shown to have a role in improving outcomes.[121] Diuretic treatment is effective in reducing fluid overload in all types of heart failure.[13] ACE inhibitors, beta-adrenoceptor blocking agents and mineralocorticoid receptor antagonists have shown prognostic benefit in patients with heart failure with reduced ejection fraction, but, to date, the same survival gains have not been shown in trials of heart failure with preserved ejection fraction.[122] Recommended therapies are often underutilised and only a small proportion of heart failure patients receive optimal treatment.[123]

An important aspect of good management is long-term monitoring. Monitoring has the potential to optimise treatment for heart failure by identifying patients who do and patients who do not need further drug treatment and can improve patient quality of life, both in terms of physical and emotional well-being.[124]

Description of the intervention and why it is important to do this review

Remote monitoring, a collective term for TM and STS, of heart failure is increasingly becoming an option for patients as a result of advancing technology and increasing familiarity with its use. RM aims to collect and transmit physiological data through devices in the patient's own home that could potentially increase early detection of clinical deterioration, improve patient's quality of life and decrease health-care delivery costs.

There have been a number of systematic reviews and meta-analyses on the effectiveness of RM. In the previous 5 years, there have been 15 meta-analyses and four in 2018 alone.[125–128] Findings from previous reviews have been inconsistent, although most favour using RM to reduce all-cause hospital admission. Primary research continues to be undertaken; in the preceding year, a further five studies have been published in this field.[129–136] Two meta-analyses have been prominent in this research area. The first by Pandor *et al.*[137] was published in 2013 as part of a Health Technology Assessment programme, and updated earlier reviews. The second, in 2015, by Inglis *et al.*,[73] was a Cochrane review, which also updated earlier reviews, and was selected as the main source of evidence for the 2018 NICE CHF guideline update.[13] These two systematic reviews examined broadly the same studies, although Inglis *et al.*[73] included only RCTs. Both reviews reported trends towards RM reducing all-cause

mortality and all-cause hospital admission, although, for Pandor *et al.*,[137] it was inconclusive. They varied in their findings for heart failure-related hospital admission. Since the publication of Inglis *et al.*,[73] two further large RM studies have reported findings: the Telemedical Interventional Management in Heart Failure II (TIM-HF2)[129,130] trial, with the second-largest number of participants to date, and the Better Effectiveness After Transition – Heart Failure (BEAT-HF)[138,139] trial, with the fourth-largest number of participants to date.

The 2010 NICE guideline[70] did not recommend the use of RM for management of CHF because it was unclear whether any of the reported benefits were due specifically to RM or to additional monitoring in general. However, NICE did recommend further research into the effectiveness of home monitoring for patients with CHF. Despite a large number of studies since 2010, the latest NICE guideline update in 2018[13] also did not recommend the use of RM for management of CHF because of lack of evidence of effectiveness. A further research recommendation for this area was not included in the 2018 guideline. NICE explain that this was because of the rapidly advancing nature of technology in the field, and the lack of any plateau in terms of the technology available to clinicians, which makes it difficult to future-proof any further research recommendations. Other factors preventing NICE from granting approval are the lack of consensus between manufacturers about the appropriate interface and between clinicians about what physiological parameters should be measured.

However, the NICE CHF guideline of 2018 does acknowledge that developments in information technology and in the use of telephone-based and direct TM technologies have the potential to improve further the delivery of health care. The NHS *Technology Enabled Care Services: Resource for Commissioners*,[71] in meeting the NHS *Five Year Forward View*,[72] highlights RM of vital health signs as a key enabler in detecting deterioration in a patient's health.

Therefore, despite the lack of NICE recommendations for the use of RM, the potential for RM technology is recognised. Widespread use of smart technology and further developments over time will mean that the question of whether or not RM for CHF is effective will continue to be clinically relevant.

Objective

The objective of this study was to evaluate the clinical effectiveness of RM (home TM and/or STS) interventions, compared with standard care, in adults with heart failure for all-cause mortality, all-cause hospital admission, heart failure-related hospital admission, length of stay, health-related quality of life, adherence, acceptability, heart failure knowledge and self-care in RCTs. This will update the existing systematic review by Inglis *et al.*[73]

Methods

This systematic review was reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[140] The protocol was registered with PROSPERO (CRD42019134922).

Search strategy

The search strategy was based on the search strategies published in Inglis *et al.*[73] Searches were conducted in the Cochrane Central Register of Controlled Trials, Ovid® (Wolters Kluwer, Alphen aan den Rijn, the Netherlands) MEDLINE® ePub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE, EMBASE™ (Elsevier, Amsterdam, the Netherlands), Cumulative Index to Nursing and Allied Health Literature, Science Citation Index Expanded (Clarivate Analytics, Philadelphia,

PA, USA), Conference Proceedings Citation Index – Science (Clarivate Analytics), Allied and Complementary Medicine Database, and the Institute of Electrical and Electronic Engineers' digital library (IEEE *Xplore*®, Institute of Electrical and Electronic Engineers, Piscataway, NJ, USA). No restriction was made for language or publication type. All publications from January 2015 to February 2019 were considered for inclusion.

Study selection

Two reviewers (JM and NP) screened the title and abstract of publications independently, to identify potentially relevant studies. Considering the full text of these publications, two reviewers (JM and NP) selected studies independently to be included in the review by using predetermined inclusion criteria. When a relevant study was identified from a conference abstract, the study was included provided a full-text peer-reviewed publication was available, even if it was published after February 2019. In all cases, disagreements about study inclusion were resolved by consensus; a third reviewer was consulted if disagreements persisted.

All studies included by Inglis *et al.*[73] were included in the review, in addition to new studies meeting the same inclusion criteria, as outlined in the following section.

Inclusion criteria

Study design

All RCTs that evaluated interventions of non-invasive TM or STS compared with usual post-discharge care.

Participants

- Adults (aged ≥ 18 years) with a definite diagnosis of heart failure living in the community [including a relative's home, but excluding nursing homes or convalescence (rehabilitation) homes].
- Participants may be recently discharged from an acute setting or already managed in the community.
- No restriction on sex or ethnicity.
- Studies with participants who had general cardiac disorders were excluded.

Intervention

- Telemonitoring (non-invasive): using patient-initiated external electronic devices remotely, with transfer of physiological data from the patient to the health-care provider by digital/broadband/satellite/wireless or Bluetooth® (Bluetooth Special Interest Group, Kirkland, WA, USA) transmission.
- Structured telephone support: monitoring or self-monitoring of telephone contact between patients and health-care providers using simple telephone technology, although data may be collected by and stored on computers. Data reported to be symptoms and/or physiological data. Studies of STS to include patients with access to touch-tone telephones.
- Intervention to be delivered as the only aftercare.
- Intervention to be targeted towards patients, rather than caregivers.
- Studies with interventions that included home visits by specialised heart failure health-care professionals or study personnel for the purpose of education or clinical assessment, other than an initial visit to set up equipment, were excluded.

Control/comparator

Usual care was defined as standard post-discharge care without intensified attendance at cardiology clinics or clinic-based heart failure disease management programme, or home visits by specialised heart failure health-care professionals or study personnel for the purpose of education or clinical assessment, other than an initial visit to set up equipment.

Studies with any previous exposure to TM or STS for the intervention or usual-care arms prior to the start of the study were excluded.

Outcome(s)

- Primary outcomes: all-cause mortality, all-cause hospital admission (at least once during the follow-up period), heart failure-related hospital admission (at least once during the follow-up period).
- Secondary outcomes: length of stay (days in hospital), health-related quality of life (assessed by a validated questionnaire), adherence (compliance), acceptability (satisfaction and usability), heart failure knowledge and self-care.

Studies that did not report any data in an extractable format for the above outcomes were excluded.

Data extraction and quality assessment

Data extraction and methodological quality assessment were conducted by one reviewer and independently checked by a second reviewer for accuracy. A data extraction form was used to pilot an initial sample of 10 studies, before proceeding to extract data for all studies. Extracted data included participant details (age, sex, ethnicity, autonomy, comorbidities), study details (design type, country, intervention and control details, follow-up period, control group, source of funding) and outcome data.

The methodological quality of studies was assessed using the same criteria as Inglis *et al.*,[73] which used the Cochrane Risk of Bias tool.[141] This considers potential biases in studies owing to selection bias (random sequence generation, allocation concealment), blinding of outcome assessors, incomplete outcome data and selective reporting. Blinding of participants is not feasible for this type of intervention; therefore, only blinding of outcome assessment was assessed. Methodological quality was assessed for the primary outcomes only because of the lack of reporting for secondary outcomes. Publication bias (small-study effect) was explored using funnel plots.[142]

Disagreements about extracted data and assessments of methodological quality were resolved by discussion or referral to a third reviewer.

Data analysis

For the primary outcomes (all-cause mortality, all-cause hospital admission and heart failure-related hospital admission), the number of people who had an event at the end of the study follow-up in each arm were pooled in a meta-analysis using a fixed-effects model based on the Mantel–Haenszel method and specifying a RR effect measure, with 95% CIs.[142]

A fixed-effects model, based on the inverse variance method, was used to pool quality-of-life data at the end of the trial using the SMD as effect measure. When required, data were inverted to ensure that all questionnaire scores had the same direction of effect. The standard error (SE) of the SMD was estimated from the data using methods derived from the Cochrane handbook.[142] The correlation coefficient was assumed to be 0.5.[143] When it was not possible to calculate the SE, it was imputed using the average of the SEs from studies using similar quality-of-life questionnaires.

Owing to the variation in data reported for length of stay, adherence, acceptability, heart failure knowledge and self-care, it was not possible to pool these data, so they were reported narratively, as in Inglis *et al.*[73]

Statistical heterogeneity was measured using the I^2 statistic.[142]

Subgroup analysis

In line with Inglis *et al.*,[73] we investigated potential causes of heterogeneity using subgroup analysis:

- Technology – comparison of:
  - telephone calls
  - videophone
  - interactive voice response – a manual input of data using a telephone keypad in response to questions from a computerised interactive voice response system and computer-assisted telephone interviewing
  - complex/clinical TM – automatic transmission of physiological data from a measuring device to a central server via telephonic, satellite or broadband capabilities for interpretation by the health-care team
  - mobile phones or personal digital assistant (PDA) – automatic transmission of physiological data from a measuring device to a mobile phone or PDA.
- Telemonitoring intensity – office hours (i.e. Monday–Friday, 09.00–17.00), compared with 24 hours per day, 7 days per week.
- Structured telephone support focus – clinical monitoring of physiological data with clinical support, compared with self-management.
- Publication date – comparisons between pre 2000, 2000–7, 2008–9 and post 2010. The year 2000 marks significant developments in heart failure treatments. The NICE CHF guideline was updated in 2007 and a new guideline was issued in 2010. The latest update of the NICE heart failure guidelines in 2018 will not have had sufficient time to show any effect.[13]
- Mean/median age – < 70 years, compared with ≥ 70 years.

Meta-regression was conducted for the primary outcomes to investigate whether or not the effect size depended on the average age of patients in the study or publication date (variables on a continuous scale).

Owing to the considerable heterogeneity found in the quality-of-life data, the robustness of the pooled results was tested using a random-effects model as a post hoc analysis.

Sensitivity analysis

Prespecified sensitivity analyses were performed to assess if the effect estimates were sensitive to the length of follow-up. Analyses were restricted to studies with follow-up periods of > 6 months.

Post hoc sensitivity analyses were conducted for the quality-of-life outcome to ensure that our effect estimates were not sensitive to our choice of questionnaire, our choices of included data and imputations. Analyses were rerun using an alternative imputation of the SE, based on all other included studies, rather than just those based on the same quality-of-life questionnaire, and, in a separate analysis, excluding studies for which imputed data had been used.

All analyses were carried out using Stata® version 14.236 (StataCorp LP, College Station, TX, USA) and/or RevMan version 5.337 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Search results

The search identified 3013 records, from which 12 new studies[129–136,138,139,144–151] met the inclusion criteria and could be added to the existing 41 studies identified by Inglis *et al.*[73] (*Figure 3*).

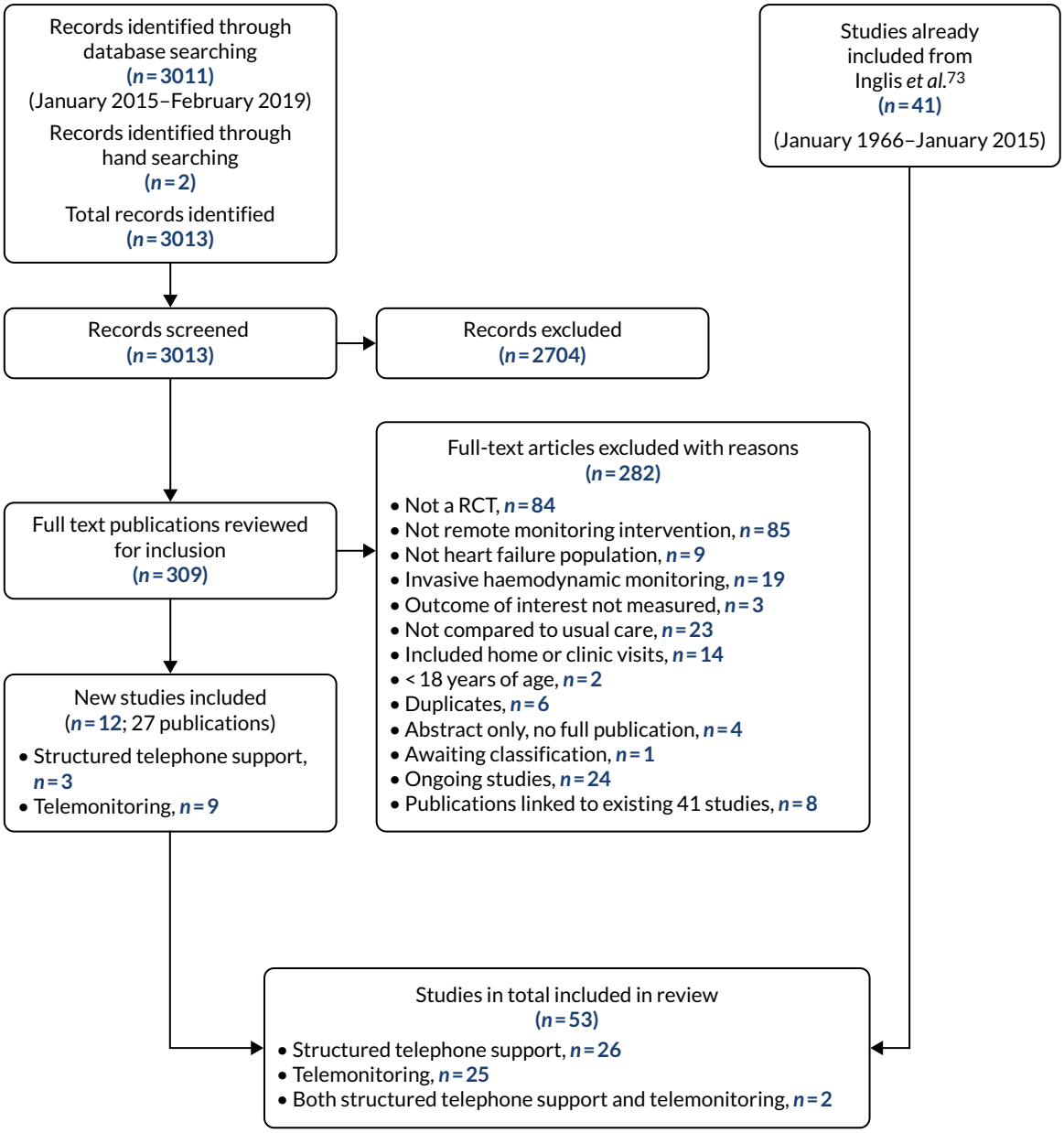


FIGURE 3 Flow chart of study selection.

Study characteristics

The characteristics of the 12 new included studies are provided in *Tables 17* and *18*. Of the 12 new included studies, three studies examined STS[144–148] and nine studies examined TM.[129–136,138,139,149–151] The characteristics of the 41 existing studies are provided in Inglis *et al.*[73] In STS studies, the total number of patients increased to 10,296, and in TM studies, the total number of patients increased to 8329, compared with 9332 and 3860, respectively, in Inglis *et al.*[73] Study sample sizes ranged from 34 to 1653 participants in STS studies, and from 20 to 1571 participants in TM studies.

Risk of bias

We considered the methodological quality of the 12 new included studies (*Figure 4*). Two studies[131,132,147,148] were assessed as being of high quality, as they were deemed to be at 'low' risk of bias across all domains. The majority of studies were assessed as being at low risk of bias for random sequence generation, allocation concealment and selective reporting. However, all studies, bar two, were assessed as having an unclear or high risk of bias for blinding of outcome assessment. Inglis *et al.*[73] assessed four studies as being at low risk of bias across all domains.[152–155]

TABLE 17 Study characteristics (12 new included studies)

Study (first author and year of publication)	Study name	RM type	Country	Total number of patients	RM intervention description	Comparator	Follow-up duration (months)	Study primary outcome	Study secondary outcome
Bekelman 2015[144]	PCDM for Heart Failure	STS	USA	392	• Patient self-care support • Health Buddy: LCD screen and four large buttons transmits via the phone line shared with the conventional telephone line	Usual care	12	• Change in HF-specific health status	• All-cause hospitalisations • Depressive symptoms • All-cause mortality • Patients' self-management of CHF • Adherence to prescribed medications • Proportion of patients with guideline-concordant care • Cost-effectiveness of the intervention
Dang 2017[145,146]	–	STS	USA	61	• Mobile phone-based disease management programme • Patients weigh themselves daily and use the mobile phone to answer questions • Information stored on server database • Triggers of any deterioration or worsening HF, the patient received a message to contact the study co-ordinator	Usual care	3	• HF knowledge • Self-efficacy for managing HF • Self-care behaviour • Health-related quality of life	–

continued

TABLE 17 Study characteristics (12 new included studies) (*continued*)

Study (first author and year of publication)	Study name	RM type	Country	Total number of patients	RM intervention description	Comparator	Follow-up duration (months)	Study primary outcome	Study secondary outcome
Karhula 2015[149]	Renewing Health Finland	TM	Finland	269	• Health coaching over mobile phones and self-monitoring of health parameters with the help of a remote patient monitoring system • Specific mobile phone software with Bluetooth-connected measurement devices	Usual care	12	• Health-related quality of life • HbA_{1c} level (diabetic patients)	• Blood pressure • Weight • Lipid measures • Organisational and economic issues
Koehler 2018[129,130]	TIM-HF2	TM	Germany	1571	• Daily transmission of data using wireless system with digital tablet (bodyweight, systolic and diastolic blood pressure, heart rate, analysis of the heart rhythm, peripheral capillary oxygen saturation and a self-rated health status) • Monthly structured telephone contact for HF education • Clinic visits at baseline and at 3, 6, 9 and 12 months	Usual care	12	Days (%) lost because of unplanned cardiovascular hospital admission or all-cause mortality	• All-cause mortality • Cardiovascular mortality • Days (%) lost because of unplanned cardiovascular hospitalisations • Days (%) lost because of HF hospitalisations • Health-related quality of life • Change in the levels of NT-proBNP and of MR-proADM

Study (first author and year of publication)	Study name	RM type	Country	Total number of patients	RM intervention description	Comparator	Follow-up duration (months)	Study primary outcome	Study secondary outcome
Kotooka 2018[131,132]	HOMES-HF	TM	Japan	183	Electronic scale with a body composition metre, a sphygmomanometer and a device called a 'receiver', which received acquired physiological data wirelessly and transmitted the data to the central web server via the internet	Usual care	15	• All-cause mortality • HF hospitalisation	• All-cause mortality • Cardiovascular mortality • All-cause hospitalisation • Cardiovascular hospitalisation • Worsening HF hospitalisation • Worsening of HF symptoms • Cost of medical care • Worsening of LVEF, NT-pro BNP, high-sensitivity C-reactive protein, pentraxin 3, high sensitivity cardiac troponin T or high-molecular-weight adiponectin • Changes in the Mini Mental State Examination, General Self-Efficacy Scale, Minnesota Living With Heart Failure or the PHQ-9 scores • Adherence to medication

continued

TABLE 17 Study characteristics (12 new included studies) (*continued*)

Study (first author and year of publication)	Study name	RM type	Country	Total number of patients	RM intervention description	Comparator	Follow-up duration (months)	Study primary outcome	Study secondary outcome
Olivari 2018[133]	Renewing Health Italy	TM	Italy	399	Personal Health System, composed of a wearable Wrist Clinic device and a digital weight scale for clinical data collection	Usual care	12	All-cause mortality or at least one hospitalisation for HF	• All-cause mortality • All-cause hospitalisation • HF hospitalisation • Duration of hospitalisations • Number of scheduled/ urgent outpatient controls • Health-related quality of life
Ong 2016[138,139]	BEAT-HF	TM	USA	1437	Three components: 1. Pre-discharge HF education 2. Regularly scheduled telephone coaching 3. Home TM of weight, blood pressure, heart rate and symptoms. Devices automatically transmitted data back to central servers for TM review	Usual care	6	All-cause re-admission rate (180 day)	• All-cause re-admission rate (30 days) • Mortality (30 and 180 days) • ED visits • Hospital days • Hospital costs • Health-related quality of life

Study (first author and year of publication)	Study name	RM type	Country	Total number of patients	RM intervention description	Comparator	Follow-up duration (months)	Study primary outcome	Study secondary outcome
Pedone 2015[150]	–	TM	Italy	96	• Office hours • Measurement devices equipped with a transmitter and an Android-based smartphone (Android; Open Handset Alliance and Google Inc., Mountain View, CA, USA) that receives from the transmitter the readings from the measurement instruments, and communicates the readings to the central web-based system	Standard care	6	All-cause hospital admission or all-cause mortality (180 days)	–
Pérez-Rodríguez 2015[151]	–	TM	Mexico	40	• Digital aneroid sphygmomanometer, a floor scale and mobile phone. All the devices provided had access to a wireless personal area network through Bluetooth, which allowed for voice and data transmission • Receiving platform located in the hospital. If any changes in the monitored parameters of the patient were detected, the nurse would immediately notify the doctor so that new instructions could be issued to the patient	Traditional	3	• Reduction of decompensation risk • Emergency room visits • Health-care costs due to chronic cardiac failure	–

continued

TABLE 17 Study characteristics (12 new included studies) (*continued*)

Study (first author and year of publication)	Study name	RM type	Country	Total number of patients	RM intervention description	Comparator	Follow-up duration (months)	Study primary outcome	Study secondary outcome
Ritchie 2016[147,148]	E Coach	STS	USA	511	• Interactive voice response – enhanced care transition intervention that monitors patients at home using their personal telephone • Web-based 'dashboard' of interactive voice responses that alert care transition nurses of patient/caregiver concerns after discharge	Usual care	1	All-cause rehospitalisation (30 days)	• All cause rehospitalisation and mortality • Community tenure
Smeets 2018[134]	Cardio-Coach	TM	Belgium	24	Two-way communication platform connected to RM devices. All vital signs measurements were transmitted automatically to the CardioCoach application, without manual patient input	Usual care	6	• User experience • Adherence • Call centre statistics • Algorithm performance • Number of patients on guideline-recommended medication dose for β-blocker and ACE inhibitors (3 and 6 months)	–

Study (first author and year of publication)	Study name	RM type	Country	Total number of patients	RM intervention description	Comparator	Follow-up duration (months)	Study primary outcome	Study secondary outcome
Wagenaar 2019[135,136]	e-Vita HF	TM	The Netherlands	450	• Online web-based platform for self-management of HF • Used in conjunction with heart matters website (www.heartfailurematters.org/en_GB/; accessed 29 January 2021) for advice • Monitored results automatically forwarded to the platform • Platform automatically sends alerts if prespecified limits are breached	Usual care	12	Self-care	• Health-related quality of life • HF knowledge • Satisfaction of HF care • All-cause hospitalisations • HF-related hospitalisations • Cardiovascular hospitalisations • Number of days in hospital • Health-care costs

BEAT-HF, Better Effectiveness After Transition – Heart Failure; ED, emergency department; HF, heart failure; LCD, liquid-crystal display; MD-proADM, mid-regional pro-adrenomedullin; PCDM, Patient-Centered Disease Management; PHQ-9, Patient Health Questionnaire-9 items; TIM-HF2, Telemedical Interventional Management in Heart Failure II.

TABLE 18 Patient characteristics (12 new included studies)

Study (first author and year of publication)	Study name	RM type	Age (years)[a]	Sex (male %)	NYHA class (%)	Acute or stable	Inclusion criteria
Bekelman 2015[144]	PCDM	STS	68	96.60	NR	Mixed acute and stable	• Primary care visit during the prior 12 months with a HF diagnosis code in the VA-electronic health record • Scoring < 60 on the Kansas City Cardiomyopathy Questionnaire
Dang 2017[145,146]	–	STS	55.3 ± 9.8	39	Class I: 47.5, class II: 37.7, class III or IV: 14.8	Stable	• Age > 18 years • Ability to speak and read English or Spanish • Anticipated survival ≥ 6 months • No previous history of unstable coronary syndromes • No end-stage HF • No heart transplantation
Karhula 2015[149]	Renewing Health Finland	TM	69.1 ± 9.1	66.2	NR	Stable	• Diagnosis of ischaemic heart disease, heart failure, or both • Diabetic patients were recruited based on a diagnosis of type 2 diabetes mellitus • Age > 18 years • Ability to fill in questionnaires in Finnish • Ability to use the RPM system and the devices provided • Adequate cognitive capacities to participate • Able to walk
Koehler 2018[129,130]	TIM-HF2	TM	70	70	Class I: 1, class II: 52, class III: 47	Discharged in previous 12 months	• Patients been admitted to hospital for worsening heart failure within 12 months • NYHA class II or III • LVEF of ≤ 45%
Kotooka 2018[131,132]	HOMES-HF	TM	66	60	Class II: 78, class III: 22	Acute	• Aged ≥ 18 years • NYHA functional class II or III HF • Discharged or scheduled to be discharged following admission for acute HF or acute decompensated CHF within 30 days of enrolment

TABLE 18 Patient characteristics (12 new included studies) (*continued*)

Study (first author and year of publication)	Study name	RM type	Age (years)[a]	Sex (male %)	NYHA class (%)	Acute or stable	Inclusion criteria
Olivari 2018[133]	Renewing Health Italy	TM	79.9	64	Class II: 48, class III: 47, class IV: 5	Acute	• Patients aged > 65 years • Hospitalised in the previous 3 months for HF • LVEF of < 40% or > 40% plus BNP of > 400 pg/ml (or NT-proBNP of > 1500 pg/ml)
Ong 2016[138,139]	BEAT-HF	TM	73 (median)	53.8	Class III or IV: 61.2[b]	Acute	• Language: English, Spanish, Persian, Russian • Individuals admitted as hospital inpatients or on observation status • Aged ≥ 50 years • Receiving active treatment for decompensated heart failure (defined as initiation of, or an increase in, diuretic treatment) • Expected to be discharged to their home
Pedone 2015[150]	–	TM	80 ± 7	39	Class II: 32, class III: 57, class IV: 11	Mixed acute and stable	• Aged ≥ 65 years • Diagnosis of HF
Pérez-Rodríguez 2015[151]	–	TM	68.5	65	NR	Stable	• Male and female diagnosed with HF • NYHA class IV • Live within coverage and mobile phone signal zone
Ritchie 2016[147,148]	E Coach	TM	63 ± 12	51.4	NR	Acute	• Admitted from home with CHF or COPD • Estimated prognosis of > 6 months • English-speaking • Have a telephone • Expected to be discharged to home
Smeets 2018[134]	CardioCoach	TM	61.75	62.3	Class II: 41.8, class III: 45.9	Acute	• Diagnosed patients with HF initiation of β-blocker and/or ACE inhibitor therapy • Or patients with known HF but on suboptimal dosage of β-blocker and/or ACE inhibitor therapy

continued

TABLE 18 Patient characteristics (12 new included studies) (*continued*)

Study (first author and year of publication)	Study name	RM type	Age (years)[a]	Sex (male %)	NYHA class (%)	Acute or stable	Inclusion criteria
Wagenaar 2019[135,136]	e-Vita HF	TM	66.8 ± 11.0	74.2	Class I: 44, class II: 36, class III: 14, class IV: 6[c]	Stable	• Diagnosed with HF for at least 3 months • Sufficient cognitive and physical function (i.e. able to fill out the questionnaires and perform blood pressure measurements and weighing) • Aged > 18 years

BEAT-HF, Better Effectiveness After Transition – Heart Failure; COPD, chronic obstructive pulmonary disease; HF, heart failure; NR, not reported; PCDM, Patient-Centered Disease Management; RPM, remote patient monitoring; TIM-HF2, Telemedical Interventional Management in Heart Failure II; VA, veterans' affairs.
a Reported as mean ± standard deviation unless otherwise stated.
b At enrolment (varies to baseline).
c Patient-reported data for 284 patients.

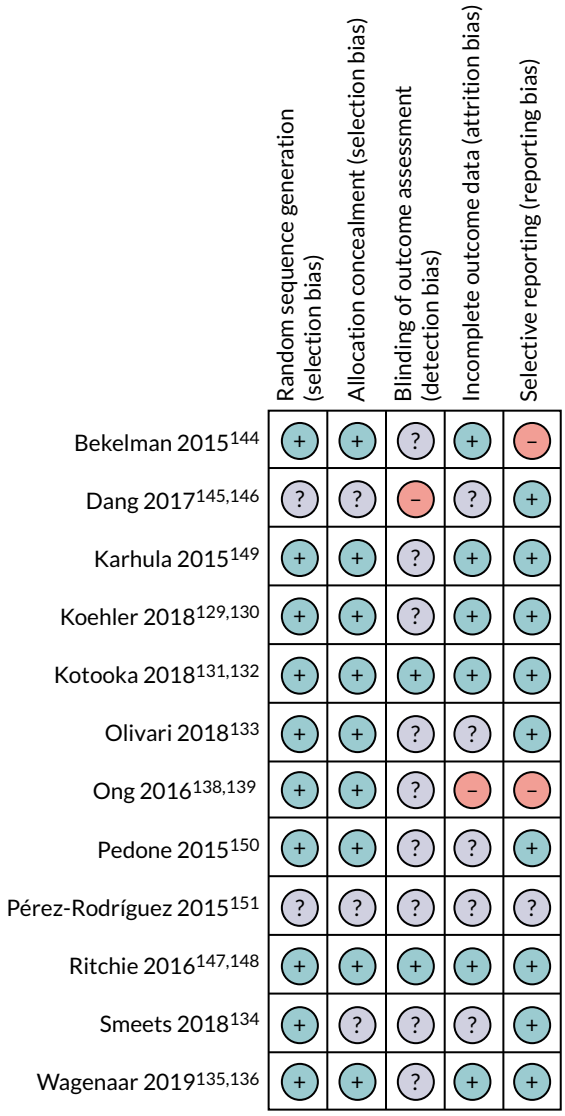


FIGURE 4 Risk-of-bias summary (12 new included studies).

Combining the risk-of-bias assessments for the 12 new included studies with the 39 existing studies from Inglis *et al.*[73] in a risk-of-bias graph (*Figure 5*) resulted in little variation from the previous graph reported by Inglis *et al.*[73] Overall, for the majority of risk-of-bias domains, studies were split between having a low or unclear risk of bias, although, for selective reporting, > 80% of studies were considered to be at low risk of bias. Few studies were considered to be at high of risk of bias in any domain, except for attrition bias, for which approximately 25% of studies were considered to be at high risk of bias.

We considered publication bias for all 53 studies based on the primary outcomes and, similar to Inglis *et al.*,[73] found evidence of strong publication bias (*Figure 6*).

All-cause mortality

Nine of the 12 new included studies reported data for all-cause mortality.[129–133,135,136,138,139,144,147,148,150,151] The data from these studies were pooled with data from the existing 39 studies in Inglis *et al.*[73] (*Figure 7*). Based on all 51 studies, when compared with usual care, RM reduced mortality among patients with heart failure (STS: RR 0.85, 95% CI 0.76 to 0.96; $I^2 = 0\%$; TM: RR 0.82, 95% CI 0.73 to 0.92; $I^2 = 20\%$).

Subgroup analyses to compare between technologies used or by the focus of the monitoring did not show any significant difference between groups. For these analyses and subgroup analysis by year of publication, most of the studies fell into one subgroup; therefore, this subgroup was similar to the overall findings for STS and TM. Subgroup analysis comparing the average age of patients (< 70 vs. ≥ 70 years) found that, for nine STS studies with patients aged ≥ 70 years, the pooled result was no longer significant, although the difference between groups was not significant ($p = 0.82$). The opposite effect was seen in

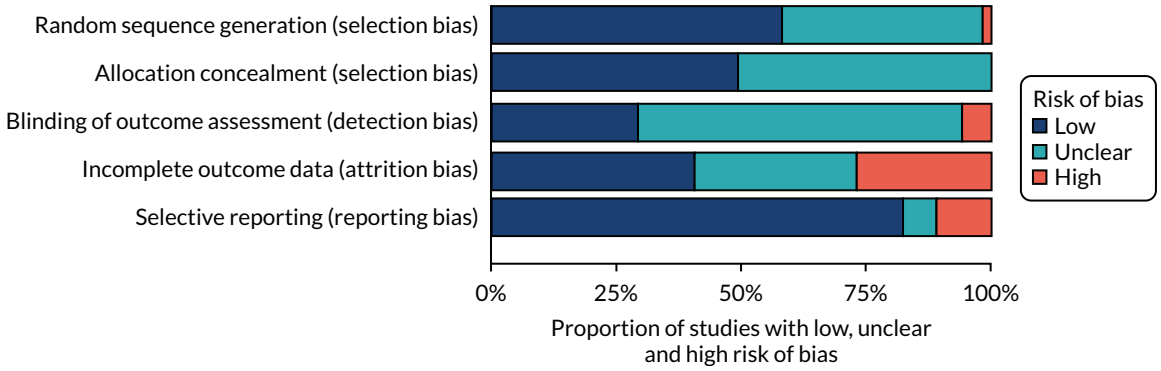


FIGURE 5 Risk-of-bias graph (all 53 studies).

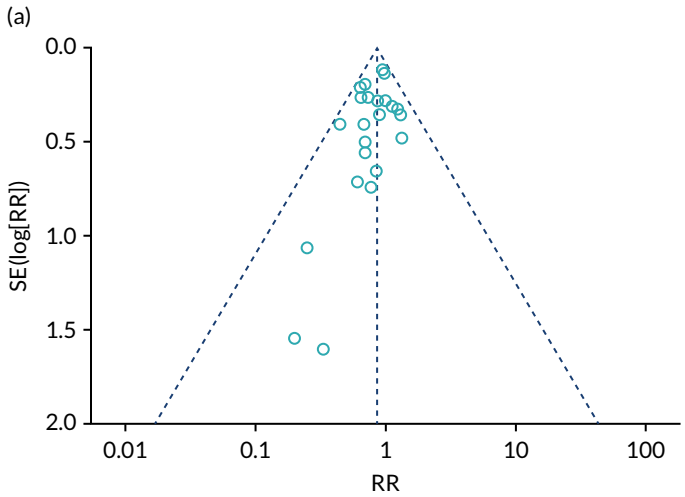


FIGURE 6 Funnel plots. (a) Funnel plot comparison for all-cause mortality for STS, (b) funnel plot comparison for all-cause mortality for TM, (c) funnel plot comparison for all-cause hospital admission for STS, (d) funnel plot comparison for all-cause hospital admission for TM, (e) funnel plot comparison for heart failure hospital admission for STS and (f) funnel plot comparison for heart failure hospital admission for TM. (*continued*)

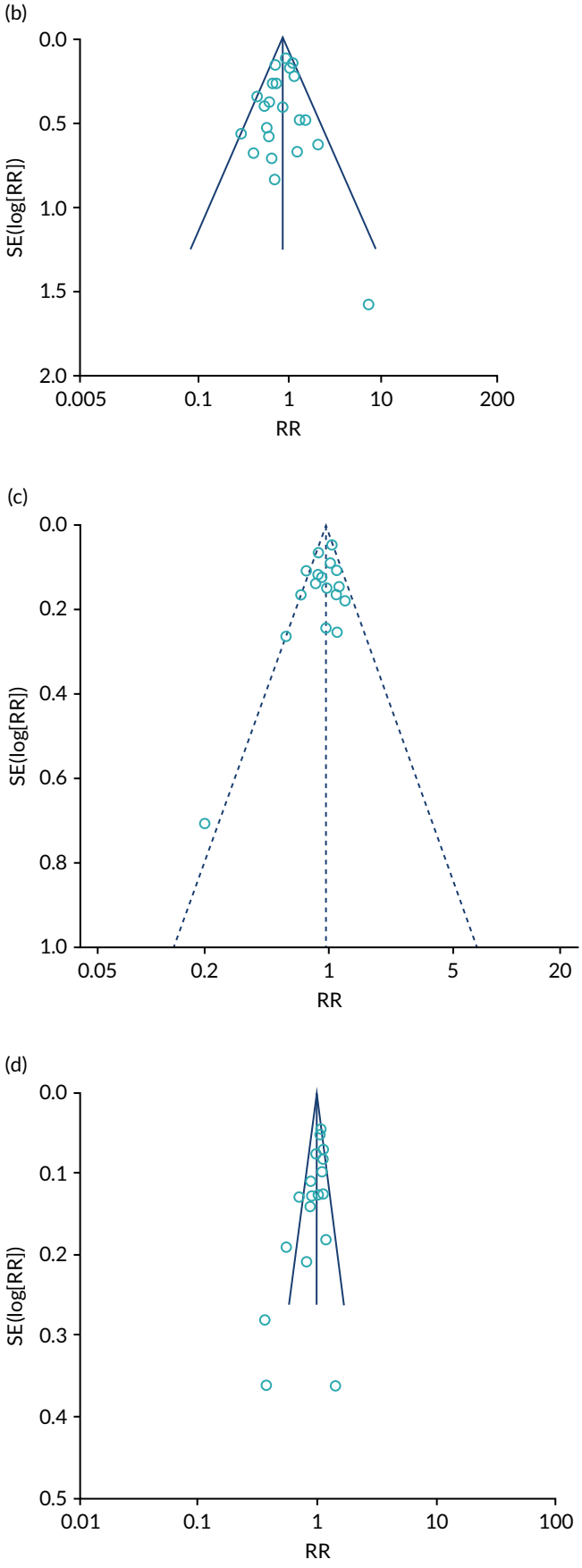


FIGURE 6 Funnel plots. (a) Funnel plot comparison for all-cause mortality for STS, (b) funnel plot comparison for all-cause mortality for TM, (c) funnel plot comparison for all-cause hospital admission for STS, (d) funnel plot comparison for all-cause hospital admission for TM, (e) funnel plot comparison for heart failure hospital admission for STS and (f) funnel plot comparison for heart failure hospital admission for TM. (*continued*)

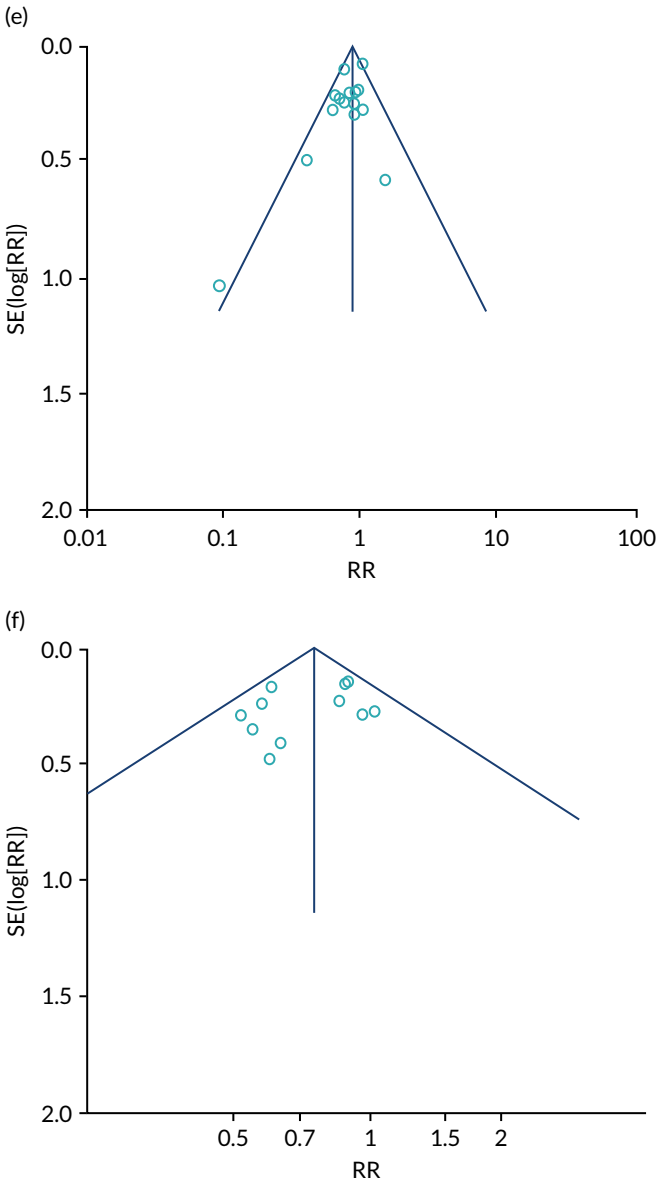


FIGURE 6 Funnel plots. (a) Funnel plot comparison for all-cause mortality for STS, (b) funnel plot comparison for all-cause mortality for TM, (c) funnel plot comparison for all-cause hospital admission for STS, (d) funnel plot comparison for all-cause hospital admission for TM, (e) funnel plot comparison for heart failure hospital admission for STS and (f) funnel plot comparison for heart failure hospital admission for TM.

12 TM studies with patients < 70 years, where for this group, the effect was no longer significant, although again the difference between groups was not significant ($p = 0.56$). Sensitivity analyses excluding studies with < 6 months of follow-up did not change the overall findings for STS, and, for TM, the RR was similar, but no longer significant (RR 0.87, 95% CI 0.75 to 1.00) (*Table 19*).

Meta-regression investigating whether or not the effect estimates depended on the average age of study participants or the year of publication did not find any association for either STS (publication date: $p = 0.63$, age: $p = 0.3$) or TM (publication date: $p = 0.23$; age: $p = 0.69$).

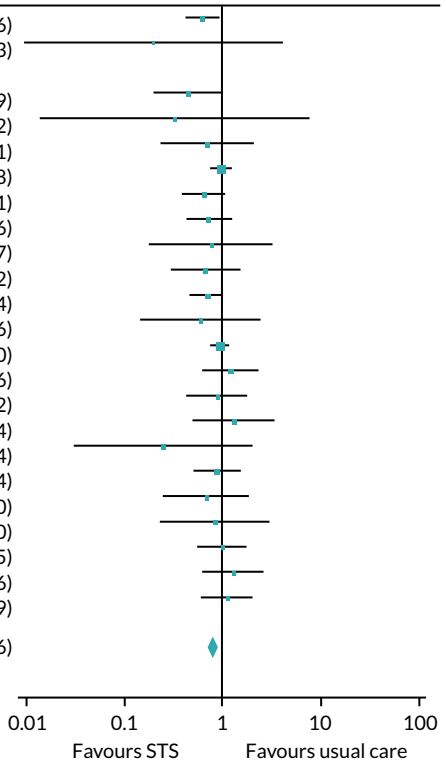
All-cause hospital admission

Six new included studies reported data for all-cause hospital admission.[131–133,135,136,138,139,147,148,150] *Figure 8* shows the pooled data from these six studies, along with data from 29 studies identified by Inglis *et al.*[73] Based on 35 studies comparing RM with usual care, the findings are inconclusive for all-cause hospital admission among patients with heart failure (STS: RR 0.95, 95% CI 0.90 to 1.0; TM: RR 0.96, 95% CI 0.91 to 1.01). Heterogeneity was moderate to substantial (STS: 44%; TM: 67%).

(a)

Study or subgroup (first author and year)	STS (*n*) Events	Total	Usual care (*n*) Events	Total	Weight (%)	RR M–H, fixed, 95% CI
Angermann 2012[156]	32	352	52	363	9.3	0.63 (0.42 to 0.96)
Baker 2011[157]	0	303	2	302	0.5	0.20 (0.01 to 4.13)
Barth 2001[158]	0	17	0	17		Not estimable
Bekelman 2015[144]	8	187	19	197	3.4	0.44 (0.20 to 0.99)
Bento and Brofman 2009[159]	0	20	1	20	0.3	0.33 (0.01 to 7.72)
Capomolla 2004[160]	5	67	7	66	1.3	0.70 (0.24 to 2.11)
Chaudhry 2010[161]	92	826	94	827	17.1	0.98 (0.75 to 1.28)
Cleland 2005[162] (STS)	27	173	20	85	4.9	0.66 (0.40 to 1.11)
DeBusk 2004[163]	21	228	29	234	5.2	0.74 (0.44 to 1.26)
DeWalt 2006[164]	3	62	4	65	0.7	0.79 (0.18 to 3.37)
Domingues 2011[165]	8	57	13	63	2.2	0.68 (0.30 to 1.52)
Galbreath 2004[166]	54	710	39	359	9.4	0.70 (0.47 to 1.04)
Gattis 1999[167]	3	90	5	91	0.9	0.61 (0.15 to 2.46)
GESICA 2005[153]	116	760	122	758	22.2	0.95 (0.75 to 1.20)
Krum 2013[168]	17	188	16	217	2.7	1.23 (0.64 to 2.36)
Laramee 2003[169]	13	141	15	146	2.7	0.90 (0.44 to 1.82)
Mortara 2009[170] (STS)	7	94	9	160	1.2	1.32 (0.51 to 3.44)
Rainville 1999[171]	1	19	4	19	0.7	0.25 (0.03 to 2.04)
Riegel 2002[172]	16	130	32	228	4.2	0.88 (0.50 to 1.54)
Riegel 2006[173]	6	70	8	65	1.5	0.70 (0.26 to 1.90)
Ritchie 2016[147,148]	4	168	5	178	0.9	0.85 (0.23 to 3.10)
Sisk 2006[155]	22	203	22	203	4.0	1.00 (0.57 to 1.75)
Tsuyuki 2004[174]	16	140	12	136	2.2	1.30 (0.64 to 2.26)
Wakefield 2008[175]	25	99	11	49	2.7	1.12 (0.60 to 2.09)
Total (95% CI)		5104		4848	100.0	0.85 (0.76 to 0.96)
Total events	496		541			

Heterogeneity: $\chi^2 = 16.24$, df = 22 ($p = 0.80$); $I^2 = 0\%$
Test for overall effect: $Z = 2.70$ ($p = 0.007$)



(b)

Study or subgroup (first author and year)	Telemonitoring (*n*) Events	Total	Usual care (*n*) Events	Total	Weight (%)	RR M–H, fixed, 95% CI
Antonicelli 2008[176]	3	28	5	29	0.9	0.62 (0.16 to 2.36)
Balk 2008[177]	9	101	8	113	1.4	1.26 (0.50 to 3.14)
Biannic 2012[178]	8	45	14	45	2.6	0.57 (0.27 to 1.23)
Blum 2014[179]	49	104	45	102	8.5	1.07 (0.79 to 1.44)
Cleland 2005[162] (TM)	28	168	20	85	5.0	0.71 (0.42 to 1.18)
de Lusignan 2001[180]	2	10	3	10	0.6	0.67 (0.14 to 3.17)
Dendale 2012[152]	4	80	14	80	2.6	0.29 (0.10 to 0.83)
Giordano 2009[181]	21	230	32	230	6.0	0.66 (0.39 to 1.10)
Goldberg 2003[182]	11	138	26	142	4.8	0.44 (0.22 to 0.85)
Koehler 2011[154]	54	354	55	356	10.3	0.99 (0.70 to 1.39)
Koehler 2018[129,130]	61	765	89	773	16.6	0.69 (0.51 to 0.94)
Kotooka 2018[131,132]	10	90	13	91	2.4	0.78 (0.36 to 1.68)
Lyngå 2012[183]	5	166	8	153	1.6	0.58 (0.19 to 1.72)
Mortara 2009[170] (TM)	8	101	9	160	1.3	1.41 (0.56 to 3.53)
Olivari 2018[133]	55	229	24	110	6.1	1.10 (0.72 to 1.68)
Ong 2016[138,139]	100	715	114	722	21.3	0.89 (0.69 to 1.13)
Pedone 2015[150]	3	47	7	43	1.4	0.39 (0.11 to 1.42)
Pérez-Rodríguez 2015[151]	0	20	0	20		Not estimable
Seto 2012[184]	3	50	0	50	0.1	7.00 (0.37 to 132.10)
Soran 2008[185]	11	160	17	155	3.2	0.63 (0.30 to 1.29)
Villani 2014[186]	5	40	9	40	1.7	0.56 (0.20 to 1.51)
Vuorinen 2014[187]	0	47	0	47		Not estimable
Wagenaar 2019[135,136]	8	150	4	150	0.8	2.00 (0.62 to 6.50)
Woodend 2008[188]	5	62	4	59	0.8	1.19 (0.34 to 4.22)
Total (95% CI)		3900		3765	100.0	0.82 (0.73 to 0.92)
Total events	463		520			

Heterogeneity: $\chi^2 = 26.37$, df = 21 ($p = 0.19$); $I^2 = 20\%$
Test for overall effect: $Z = 3.35$ ($p = 0.0008$)

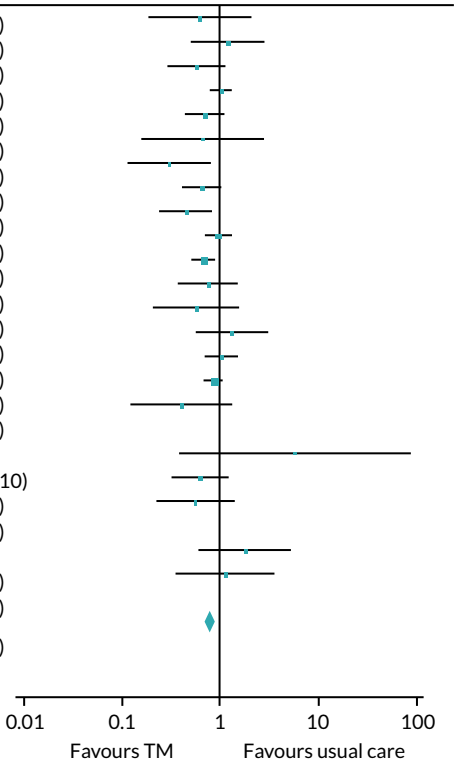


FIGURE 7 Forest plots to show RM vs. usual care on all-cause mortality. (a) STS; and (b) TM. M–H, Mantel–Haenszel.

TABLE 19 Results of analyses

Analysis	Effect estimate (95% CI)	Number of studies	I^2 (%)	Test for subgroup differences (*p*-value)
All-cause mortality (RR, < 1 favours RM)				
STS vs. usual care				
Fixed effects, Mantel–Haenszel method	0.85 (0.76 to 0.96)[a]	24	0	NA
Subgroup by technology: telephone call	0.81 (0.71 to 0.93)[a]	17	0	$p = 0.39$
Subgroup by technology: videophone	1.12 (0.60 to 2.09)	1[b]	NA	
Subgroup by technology: interactive voice response	0.93 (0.77 to 1.17)	6	0	
Subgroup by focus: clinical support	0.87 (0.96 to 0.98)[a]	19	0	$p = 0.42$
Subgroup by focus: self-management education	0.73 (0.48 to 1.10)	5	16	
Subgroup by publication year: pre 2000	0.45 (0.14 to 1.40)	2[b]	0	$p = 0.18$
Subgroup by publication year: 2000–7	0.86 (0.74 to 0.99)[a]	13	0	
Subgroup by publication year: 2008–10	1.01 (0.79 to 1.28)	4	0	
Subgroup by publication year: post 2010	0.70 (0.53 to 0.94)[a]	5	0	
Subgroup by mean/median age: < 70 years	0.96 (0.75 to 0.99)[a]	15	0	$p = 0.83$
Subgroup by mean/median age: ≥ 70 years	0.84 (0.67 to 1.04)	9	0	
Sensitivity analysis: excluding studies with < 6 months of follow-up	0.85 (0.74 to 0.99)[a]	12	0	NA
TM vs. usual care				
Fixed effects, Mantel–Haenszel method	0.82 (0.73 to 0.92)[a]	24	20	NA
Subgroup by technology: videophone	1.19 (0.34 to 4.22)	1[b]	NA	$p = 0.69$
Subgroup by technology: complex/clinical TM	0.83 (0.73 to 0.93)[a]	19	25	
Subgroup by technology: mobile phone/PDA	0.71 (0.46 to 1.11)	4	25	
Subgroup by intensity: office hours	0.70 (0.53 to 0.92)[a]	11	0	$p = 0.36$
Subgroup by focus: 24 hours per day/7 days per week	0.81 (0.69 to 0.95)[a]	10	43	
Subgroup by publication year: 2000–7	0.58 (039 to 0.86)[a]	3[b]	0	$p = 0.18$
Subgroup by publication year: 2008–10	0.81 (0.59 to 1.12)	6	0	
Subgroup by publication year: post 2010	0.86 (0.75 to 0.97)[a]	15	33	
Subgroup by mean/median age: < 70 years	0.86 (0.70 to 1.05)	12	27	$p = 0.56$
Subgroup by mean/median age: ≥ 70 years	0.80 (0.70 to 0.92)[a]	12	23	
Sensitivity analysis: excluding studies with < 6 months of follow-up	0.87 (0.75 to 1.00)	14	0	NA
All-cause hospitalisation (RR, < 1 favours RM)				
STS vs. usual care				
Fixed effects, Mantel–Haenszel method	0.95 (0.90 to 1.00)	17	44	NA
Subgroup by technology: telephone call	0.93 (0.86 to 0.99)[a]	12	51	$p = 0.08$
Subgroup by technology: videophone	0.70 (0.50 to 0.97)[a]	1[b]	NA	

continued

TABLE 19 Results of analyses (*continued*)

Analysis	Effect estimate (95% CI)	Number of studies	I^2 (%)	Test for subgroup differences (*p*-value)
Subgroup by technology: interactive voice response	1.00 (0.91 to 1.09)	4	65	
Subgroup by focus: clinical support	0.94 (0.89 to 1.00)	15	49	$p = 0.32$
Subgroup by focus: self-management education	1.08 (0.84 to 1.38)	2[b]	0	
Subgroup by publication year: pre 2000	0.57 (0.34 to 0.95)[a]	1[b]	NA	$p = 0.14$
Subgroup by publication year: 2000–7	0.93 (0.86 to 1.01)	8	0	
Subgroup by publication year: 2008–10	1.01 (0.92 to 1.10)	4	73	
Subgroup by publication year: post 2010	0.95 (0.82 to 1.09)	4	55	
Subgroup by mean/median age: < 70 years	0.95 (0.89 to 1.02)	11	52	$p = 0.83$
Subgroup by mean/median age: ≥ 70 years	0.94 (0.85 to 1.04)	6	36	
Sensitivity analysis: excluding studies with < 6 months of follow-up	0.89 (0.82 to 0.96)[a]	7	37	NA
TM vs. usual care				
Fixed effects, Mantel–Haenszel method	0.96 (0.91 to 1.01)	18	67	NA
Subgroup by technology: videophone	1.06 (0.97 to 1.16)	1[b]	NA	$p = 0.02$[a]
Subgroup by technology: complex/clinical TM	0.98 (0.93 to 1.03)	14	67	
Subgroup by technology: mobile phone/PDA	0.77 (0.63 to 0.95)[a]	3[b]	40	
Subgroup by intensity: office hours	0.84 (0.76 to 0.94)[a]	7	72	$p = 0.03$[a]
Subgroup by focus: 24 hours per day/7 days per week	0.97 (0.90 to 1.05)	9	66	
Subgroup by publication year: 2000–7	0.94 (0.79 to 1.12)	2[b]	0	$p = 0.37$
Subgroup by publication year: 2008–10	0.89 (0.79 to 1.01)	5	88	
Subgroup by publication year: post 2010	0.98 (0.93 to 1.04)	11	61	
Subgroup by mean/median age: < 70 years	0.96 (0.88 to 1.04)	9	54	$p = 0.90$
Subgroup by mean/median age: ≥ 70 years	0.96 (0.90 to 1.03)	9	77	
Sensitivity analysis: excluding studies with < 6 months of follow-up	0.94 (0.88 to 1.01)	11	71	NA
Heart failure hospitalisation (RR, < 1 favours RM)				
STS vs. usual care				
Fixed effects, Mantel–Haenszel method	0.85 (0.77 to 0.93)[a]	16	27	NA
Subgroup by technology: telephone call	0.76 (0.67 to 0.86)[a]	13	2	$p = 0.007$[a]
Subgroup by technology: interactive voice response	0.99 (0.86 to 1.14)	3[b]	0	
Subgroup by focus: clinical support	0.84 (0.76 to 0.93)[a]	15	31	$p = 0.56$
Subgroup by focus: self-management education	0.95 (0.64 to 1.39)	1[b]	NA	
Subgroup by publication year: pre 2000	0.24 (0.10 to 0.58)[a]	2[b]	48	$p = 0.002$[a]
Subgroup by publication year: 2000–7	0.78 (0.69 to 0.89)[a]	10	0	
Subgroup by publication year: 2008–10	1.02 (0.88 to 1.19)	2[b]	0	

TABLE 19 Results of analyses (*continued*)

Analysis	Effect estimate (95% CI)	Number of studies	I^2 (%)	Test for subgroup differences (*p*-value)
Subgroup by publication year: post 2010	0.79 (0.57 to 1.08)	2[b]	0	
Subgroup by mean/median age: < 70 years	0.86 (0.77 to 0.96)[a]	8	51	$p = 0.53$
Subgroup by mean/median age: ≥ 70 years	0.81 (0.67 to 0.96)[a]	8	27	
Sensitivity analysis: excluding studies < 6 months of follow-up	0.76 (0.66 to 0.88)[a]	7	0	NA
TM vs. usual care				
Fixed effects, Mantel–Haenszel method	0.74 (0.64 to 0.84)[a]	12	17	NA
Subgroup by technology: complex/clinical telemonitoring	0.79 (0.68 to 0.92)[a]	9	14	$p = 0.05$
Subgroup by technology: mobile phone/PDA	0.58 (0.44 to 0.77)[a]	3[b]	0	
Subgroup by intensity: office hours	0.72 (0.58 to 0.89)[a]	7	22	$p = 0.83$
Subgroup by focus: 24 hours/7 days per week	0.70 (0.57 to 0.86)[a]	4	14	
Subgroup by publication year: 2000–7	0.84 (0.55 to 1.30)	1[b]	NA	$p = 0.56$
Subgroup by publication year: 2008–10	0.66 (0.51 to 0.86)[a]	3[b]	41	
Subgroup by publication year: post 2010	0.76 (0.64 to 0.89)[a]	8	19	
Subgroup by mean/median age: < 70 years	0.75 (0.64 to 0.88)[a]	9	7	$p = 0.71$
Subgroup by publication year: ≥ 70 years	0.71 (0.57 to 0.89)[a]	3[b]	57	
Sensitivity analysis: excluding studies < 6 months of follow-up	0.80 (0.69 to 0.93)[a]	7	0	NA
Quality of life (SMD, > 1 favours RM) *STS vs. usual care*				
Fixed effects, inverse variance method	0.13 (0.09 to 0.18)[a]	12	86	NA
Subgroup by technology: telephone call	0.14 (0.09 to 0.18)[a]	9	90	$p = 0.78$
Subgroup by technology: videophone	0.10 (–0.14 to 0.34)	1[b]	NA	
Subgroup by technology: interactive voice response	0.07 (–0.14 to 0.27)	2[b]	0	
Subgroup by focus: clinical support	0.16 (0.11 to 0.22)[a]	8	89	$p = 0.10$
Subgroup by focus: self-management education	0.08 (0.01 to 0.16)[a]	3[b]	85	
Subgroup by publication year: 2000–7	0.09 (0.02 to 0.16)[a]	5	91	$p = 0.003$[a]
Subgroup by publication year: 2008–10	0.40 (0.23 to 0.56)[a]	3[b]	86	
Subgroup by publication year: post 2010	0.13 (0.07 to 0.19)[a]	4	75	
Subgroup by mean/median age: < 70 years	0.20 (0.15 to 0.25)[a]	10	83	$p = < 0.0001$[a]
Subgroup by mean/median age: ≥ 70 years	–0.06 (–0.15 to 0.03)	2[b]	63	
Sensitivity analysis: excluding studies < 6 months of follow-up	0.10 (0.03 to 0.17)	6	89	NA
Sensitivity analysis: using alternative EQ-5D data for Riegel *et al.*[173]	0.14 (0.10 to 0.18)[a]	12	86	NA
Sensitivity analysis: using alternative EQ-5D (single item) data for Riegel *et al.*[173]	0.13 (0.09 to 0.17)[a]	12	87	NA

continued

TABLE 19 Results of analyses (*continued*)

Analysis	Effect estimate (95% CI)	Number of studies	I^2 (%)	Test for subgroup differences (*p*-value)
Sensitivity analysis: using alternative SF-36 (mental component) data for Galbreath *et al.*[166]	0.17 (0.13 to 0.22)[a]	12	81	NA
Sensitivity analysis: using alternative imputation of SE based on mean from all studies	0.18 (0.13 to 0.22)[a]	12	82	NA
Sensitivity analysis: excluding studies with imputed data	0.19 (0.14 to 0.24)[a]	9	85	NA
Sensitivity analysis: using random effects model	0.24 (0.10 to 0.37)[a]	12	86	NA
TM vs. usual care				
Fixed effects, inverse variance method	0.24 (0.20 to 0.28)[a]	11	98	NA
Subgroup by technology: complex/clinical telemonitoring	0.26 (0.22 to 0.31)[a]	9	98	$p = 0.003$[a]
Subgroup by technology: mobile phone/PDA	0.08 (–0.04 to 0.19)	2[b]	68	
Subgroup by intensity: office hours	0.08 (–0.08 to 0..23)	3[b]	0	$p = 0.01$[a]
Subgroup by focus: 24 hours/7 days per week	0.29 (0.23 to 0.36)[a]	5	99	
Subgroup by publication year: 2000–7	0.06 (–0.07 to 0.20)	2[b]	0	$p = 0.004$[a]
Subgroup by publication year: 2008–10	0.00 (–0.27 to 0.27)	1[b]	NA	
Subgroup by publication year: post 2010	0.27 (0.22 to 0.31)[a]	8	98	
Subgroup by mean/median age: < 70 years	0.33 (0.27 to 0.39)[a]	6	99	$p = < 0.0001$[a]
Subgroup by publication year: ≥ 70 years	0.15 (0.09 to 0.21)[a]	5	95	
Sensitivity analysis: excluding studies < 6 months of follow-up	No change			NA
Sensitivity analysis: using alternative SF-36 (physical component) data for Blum and Gottlieb[179]	0.24 (0.19 to 0.28)[a]	11	98	NA
Sensitivity analysis: using alternative SF-36 (mental component) data for Blum and Gottlieb[179]	0.26 (0.22 to 0.31)[a]	11	98	NA
Sensitivity analysis: using alternative SF-36 (mental component) data for Antonicelli *et al.*[176]	0.25 (0.21 to 0.29)[a]	11	98	NA
Sensitivity analysis: using alternative SF-36 v.2 (mental component) data for Olivari *et al.*[133]	0.25 (0.21 to 0.29)[a]	11	98	NA
Sensitivity analysis: using alternative SF-36 (mental component) data for Karhula *et al.*[149]	0.23 (0.19 to 0.27)[a]	11	98	NA
Sensitivity analysis: using alternative imputation of SE based on mean from all studies	0.25 (0.20 to 0.29)[a]	11	98	NA
Sensitivity analysis: excluding studies with imputed data	0.26 (0.21 to 0.30)[a]	10	98	NA
Sensitivity analysis: using random effects model	0.25 (–0.05 to 0.55)	11	98	NA

NA, not applicable; SF-36, Short Form questionnaire-36 items.
a Indicates a statistically significant result.
b Indicates that a pooled result for three or fewer studies has been included for completeness; however, a pooled result from so few studies should be viewed with caution.

(a)

Study or subgroup (first author and year)	STS (*n*) Events	Total	Control (*n*) Events	Total	Weight (%)	RR M–H, fixed, 95% CI
Angermann 2012[156]	119	352	112	363	7.2	1.10 (0.89 to 1.35)
Bento and Brofman 2009[159]	2	20	10	20	0.7	0.20 (0.05 to 0.80)
Chaudhry 2010[161]	407	826	392	827	25.5	1.04 (0.94 to 1.15)
Cleland 2005[162] (STS)	85	173	46	85	4.0	0.91 (0.71 to 1.16)
DeBusk 2004[163]	116	228	117	234	7.5	1.02 (0.85 to 1.22)
Domingues 2011[165]	20	57	23	63	1.4	0.96 (0.59 to 1.55)
Gattis 1999[167]	17	90	30	91	1.9	0.57 (0.34 to 0.96)
GESICA 2005[153]	261	760	296	758	19.3	0.88 (0.77 to 1.00)
Krum 2013[168]	74	188	114	217	6.9	0.75 (0.60 to 0.93)
Laramee 2003[169]	49	141	46	146	2.9	1.10 (0.79 to 1.53)
Mortara 2009[170] (STS)	34	94	48	160	2.3	1.21 (0.84 to 1.72)
Riegel 2002[172]	56	130	114	228	5.4	0.86 (0.68 to 1.09)
Riegel 2006[173]	39	70	37	65	2.5	0.98 (0.73 to 1.32)
Ritchie 2016[147,148]	27	168	26	178	1.6	1.10 (0.67 to 1.81)
Sisk 2006[155]	62	203	74	203	4.8	0.84 (0.64 to 1.10)
Tsuyuki 2004[174]	59	140	51	136	3.4	1.12 (0.84 to 1.50)
Wakefield 2008[175]	41	99	29	49	2.5	0.70 (0.50 to 0.97)
Total (95% CI)		3739		3823	100.0	0.95 (0.90 to 1.00)
Total events	1468		1565			

Heterogeneity: $\chi^2 = 28.82$, df = 16 ($p = 0.03$); $I^2 = 44\%$
Test for overall effect: $Z = 1.84$ ($p = 0.07$)

RR M–H, fixed, 95% CI

0.05 0.2 1 5 20
Favours STS Favours usual care

(b)

Study or subgroup (first author and year)	Telemonitoring (*n*) Events	Total	Control (*n*) Events	Total	Weight (%)	RR M–H, fixed, 95% CI
Antonicelli 2008[176]	9	28	26	29	1.8	0.36 (0.21 to 0.62)
Biannic 2012[178]	19	45	35	45	2.5	0.54 (0.37 to 0.79)
Blum 2014[179]	80	104	74	102	5.3	1.06 (0.90 to 1.24)
Cleland 2005[162] (TM)	80	168	46	85	4.3	0.88 (0.68 to 1.13)
Dendale 2012[152]	64	80	66	80	4.7	0.97 (0.84 to 1.13)
Giordano 2009[181]	67	230	96	230	6.8	0.70 (0.54 to 0.90)
Goldberg 2003[182]	65	138	67	142	4.7	1.00 (0.78 to 1.28)
Koehler 2011[154]	192	354	179	356	12.6	1.08 (0.94 to 1.24)
Kotooka 2018[131,132]	27	90	34	91	2.4	0.80 (0.53 to 1.21)
Lyngå 2012[183]	79	166	84	153	6.2	0.87 (0.70 to 1.07)
Mortara 2009[170] (TM)	35	101	48	160	2.6	1.16 (0.81 to 1.65)
Olivari 2018[133]	141	229	62	110	5.9	1.09 (0.90 to 1.33)
Ong 2016[138,139]	363	715	355	722	24.9	1.03 (0.93 to 1.15)
Pedone 2015[150]	8	47	20	43	1.5	0.37 (0.18 to 0.74)
Seto 2012[184]	14	50	10	50	0.7	1.40 (0.69 to 2.85)
Soran 2008[185]	75	160	66	155	4.7	1.10 (0.86 to 1.41)
Wagenaar 2019[135,136]	57	150	66	150	4.7	0.86 (0.66 to 1.13)
Woodend 2008[188]	60	62	54	59	3.9	1.06 (0.97 to 1.16)
Total (95% CI)		2917		2762	100.0	0.96 (0.91 to 1.01)
Total events	1435		1388			

Heterogeneity: $\chi^2 = 52.24$, df = 17 ($p < 0.0001$); $I^2 = 67\%$
Test for overall effect: $Z = 1.48$ ($p = 0.14$)

RR M–H, fixed, 95% CI

0.05 0.2 1 5 20
Favours TM Favours usual care

FIGURE 8 Forest plots to show RM vs. usual care on all-cause hospital admissions. (a) STS; and (b) TM. M–H, Mantel–Haenszel.

Subgroup analyses of STS versus usual care by technology type suggest that telephone calls as a technology used may favour STS, as this subgroup, 12 of 17 total studies, showed a significant pooled effect (RR 0.93, 95% CI 0.86 to 0.99), although the test for subgroup difference was not significant ($p = 0.08$). All other subgroups analysed showed no difference to the overall findings in terms of direction of effect and statistical significance. A sensitivity analysis excluding studies with < 6 months of follow-up reported a statistically significant result, with reduced heterogeneity (RR 0.89, 95% CI 0.82 to 0.96; $I^2 = 37\%$).

Subgroup analyses of TM versus usual care suggest a significant subgroup difference for technologies used ($p = 0.02$), with mobile phones and PDAs now suggesting a statistically significant reduction in all-cause hospital admission (RR 0.77, 95% CI 0.63 to 0.95), whereas videophone and complex/clinical

TM remained inconclusive. Subgroup analyses for the intensity of monitoring suggest that monitoring during office hours, compared with 24 hours per day, 7 days per week, is statistically significant (RR 0.84, 95% CI 0.76 to 0.94); the test for subgroup difference was significant ($p = 0.03$). A sensitivity analysis excluding studies with shorter follow-up duration did not change the finding (see *Table 19*).

Meta-regression testing for any association between the effect estimates and the average age of study patients or year of publication found no evidence for either STS (publication date: $p = 0.68$; age: $p = 0.87$) or TM (publication date: $p = 0.6$; age: $p = 0.33$).

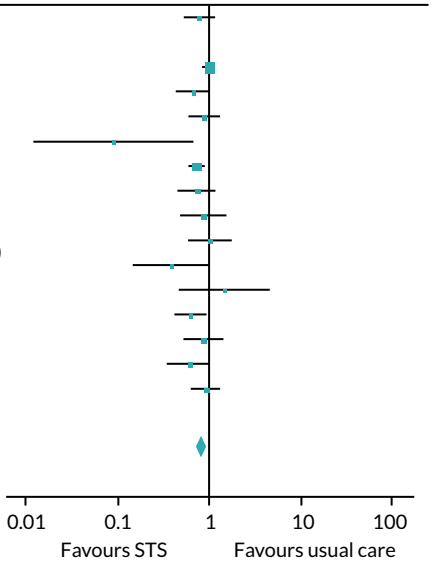
Heart failure hospital admission

Only four new included studies, all TM studies, reported data for all-cause hospital admission.[131–133,135,136,151] The data from these four studies were pooled with data from 24 studies identified by Inglis *et al.*[73] (*Figure 9*). RM compared with usual care (28 studies) reduces the rate of heart failure hospital admissions among patients with heart failure (STS: RR 0.85, 95% CI 0.77 to 0.93; $I^2 = 27\%$; TM: RR 0.74, 95% CI 0.64 to 0.84; $I^2 = 17\%$).

(a)

Study or subgroup (first author and year)	STS (*n*) Events	Total	Control (*n*) Events	Total	Weight	RR M–H, fixed, 95% CI
Angermann 2012[156]	36	352	46	363	6.1%	0.81 (0.54 to 1.22)
Barth 2001[158]	0	17	0	17		No estimable
Chaudhry 2010[161]	227	826	223	827	29.8%	1.02 (0.87 to 1.19)
Cleland 2005[162] (STS)	34	173	24	85	4.3%	0.70 (0.44 to 1.10)
DeBusk 2004[163]	38	228	43	234	5.7%	0.91 (0.61 to 1.35)
Gattis 1999[167]	1	90	11	91	1.5%	0.09 (0.01 to 0.70)
GESICA 2005[153]	128	760	169	758	22.7%	0.76 (0.61 to 0.93)
Krum 2013[168]	23	188	35	217	4.4%	0.76 (0.47 to 1.24)
Laramee 2003[169]	18	141	21	146	2.8%	0.89 (0.49 to 1.59)
Mortara 2009[170] (STS)	17	94	28	160	2.8%	1.03 (0.60 to 1.78)
Rainville 1999[171]	4	19	10	19	1.3%	0.40 (0.15 to 1.05)
Ramachandran 2007[189]	6	25	4	25	0.5%	1.50 (0.48 to 4.68)
Riegel 2002[172]	23	130	63	228	6.1%	0.64 (0.42 to 0.98)
Riegel 2006[173]	21	70	22	65	3.1%	0.89 (0.54 to 1.45)
Sisk 2006[155]	18	203	29	203	3.9%	0.62 (0.36 to 1.08)
Tsuyuki 2004[174]	37	140	38	136	5.2%	0.95 (0.64 to 1.39)
Total (95% CI)		3456		3574	100.0%	0.85 (0.77 to 0.93)
Total events	631		766			

Heterogeneity: $\chi^2 = 19.20$, df = 14 ($p = 0.16$); $I^2 = 27\%$
Test for overall effect: $Z = 3.50$ ($p = 0.0005$)



(b)

Study or subgroup (first author and year)	Telemonitoring (*n*) Events	Total	Control (*n*) Events	Total	Weight	RR M-H, fixed, 95% CI
Biannic 2012[178]	12	45	24	45	6.2%	0.50 (0.29 to 0.87)
Cleland 2005[162] (TM)	40	168	24	85	8.3%	0.84 (0.55 to 1.30)
Dendale 2012[152]	19	80	34	80	8.8%	0.56 (0.35 to 0.89)
Giordano 2009[181]	43	230	73	230	19.0%	0.59 (0.42 to 0.82)
Koehler 2011[154]	64	354	74	356	19.2%	0.87 (0.64 to 1.17)
Kotooka 2018[131,132]	19	90	20	91	5.2%	0.96 (0.55 to 1.68)
Mortara 2009[170] (TM)	18	101	28	160	5.6%	1.02 (0.60 to 1.74)
Olivari 2018[133]	79	229	43	110	15.1%	0.88 (0.66 to 1.18)
Pérez-Rodríguez 2015[151]	0	20	4	20	1.2%	0.11 (0.01 to 1.94)
Scherr 2009[190]	11	66	17	54	4.9%	0.53 (0.27 to 1.03)
Vuorinen 2014[187]	8	47	13	47	3.4%	0.62 (0.28 to 1.35)
Wagenaar 2019[135,136]	7	150	12	150	3.1%	0.58 (0.24 to 1.44)
Total (95% CI)		1580		1428	100.0%	0.74 (0.64 to 0.84)
Total events	320		366			

Heterogeneity: $\chi^2 = 13.33$, df = 11 ($p = 0.27$); $I^2 = 17\%$
Test for overall effect: $Z = 4.54$ ($p < 0.00001$)

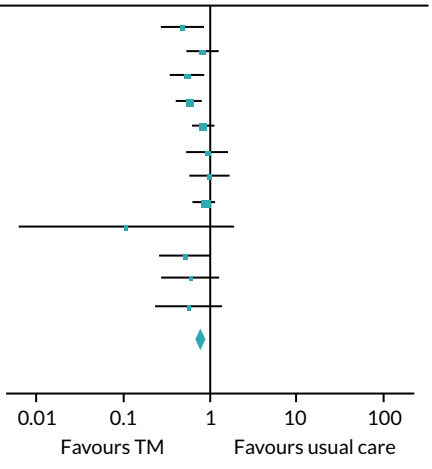


FIGURE 9 Forest plots to show RM vs. usual care on heart failure hospital admissions. (a) STS; and (b) TM. M–H, Mantel–Haenszel.

Subgroup and sensitivity analyses for STS and TM were similar. All subgroup analyses and sensitivity analyses excluding studies with < 6 months of follow-up showed the same direction of effect and statistical significance as the overall finding. Testing for subgroup difference was significant for STS only by technology used ($p = 0.007$) and year of publication ($p = 0.002$) (see *Table 19*).

Similar to the other two primary outcomes, meta-regression testing for any association between the effect estimates and the average age of study patients or year of publication found no evidence for either STS (publication date: $p = 0.13$; age: $p = 0.42$) or TM (publication date: $p = 0.6$, age: $p = 0.82$).

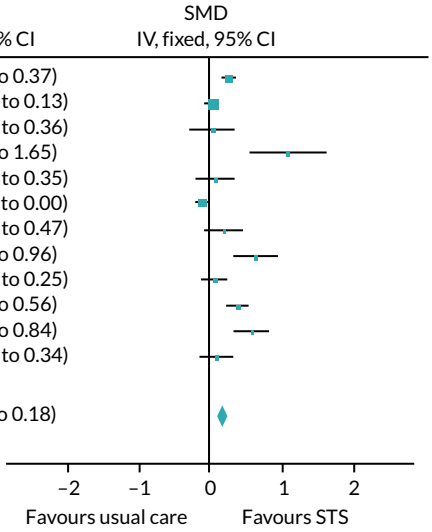
Quality of life

Nine of the 12 new included studies reported data for quality of life,[129–133,135,136,138,139,144–149] although one of these could not be pooled.[129,130] Inglis *et al.*[73] did not report a pooled result for quality of life; however, 15 studies[153–157,166,173,175,176,179,180,182,184,189,191] did report these data in a format that could be pooled with the newly acquired data. Based on 27 studies, RM, compared with usual care, improved quality of life among patients with heart failure (STS: SMD 0.13, 95% CI 0.09 to 0.18; TM: SMD 0.24, 95% CI 0.20 to 0.28; *Figure 10*). However, these results should be viewed with caution as the heterogeneity was

(a)

Study or subgroup (first author and year)	SMD	SE	Weight (%)	SMD IV, fixed, 95% CI
Angermann 2012[156]	0.27	0.05	19.7	0.27 (0.17 to 0.37)
Baker 2011[157]	0.05	0.04	30.8	0.05 (−0.03 to 0.13)
Bekelman 2015[144]	0.05	0.16	1.9	0.05 (−0.26 to 0.36)
Brandon 2009[191]	1.10	0.28	0.6	1.10 (0.55 to 1.65)
Dang 2017[145,146]	0.08	0.14	2.5	0.08 (−0.19 to 0.35)
Galbreath 2004[166]	−0.10	0.05	19.7	−0.10 (−0.20 to 0.00)
GESICA 2005[153]	0.20	0.14	2.5	0.20 (−0.07 to 0.47)
Ramachandran 2007[189]	0.65	0.16	1.9	0.65 (0.34 to 0.96)
Riegel 2006[173]	0.07	0.09	6.1	0.07 (−0.11 to 0.25)
Sisk 2006[155]	0.40	0.08	7.7	0.40 (0.24 to 0.56)
Wakefield 2008[175] (telephone)	0.59	0.13	2.9	0.59 (0.34 to 0.84)
Wakefield 2008[175] (videophone)	0.10	0.12	3.4	0.10 (−0.14 to 0.34)
Total (95% CI)			100.0%	0.13 (0.09 to 0.18)

Heterogeneity: $\chi^2 = 80.60$, df = 11 ($p < 0.00001$); $I^2 = 86\%$
Test for overall effect: $Z = 5.95$ ($p < 0.00001$)



(b)

Study or subgroup (first author and year)	SMD	SE	Weight (%)	SMD IV, fixed, 95% CI
Antonicelli 2008[176]	0.00	0.14	2.4	0.00 (−0.27 to 0.27)
Blum 2014[179]	−0.27	0.07	9.6	−0.27 (−0.41 to −0.13)
de Lusignan 2001[180]	0.27	0.28	0.6	0.27 (−0.28 to 0.82)
Goldberg 2003[182]	0.05	0.07	9.6	0.05 (−0.09 to 0.19)
Karhula 2015[149]	0.01	0.07	9.6	0.01 (−0.13 to 0.15)
Koehler 2011[154]	1.50	0.07	9.6	1.50 (1.36 to 1.64)
Kotooka 2018[131,132]	0.09	0.10	4.7	0.09 (−0.11 to 0.29)
Olivari 2018[133]	0.71	0.08	7.4	0.71 (0.55 to 0.87)
Ong 2016[138,139]	0.15	0.04	29.5	0.15 (0.07 to 0.23)
Seto 2012[184]	0.24	0.11	3.9	0.24 (0.02 to 0.46)
Wagenaar 2019[135,136]	0.02	0.06	13.1	0.02 (−0.10 to 0.14)
Total (95% CI)			100.0%	0.24 (0.20 to 0.28)

Heterogeneity: $\chi^2 = 453.46$, df = 10 ($p < 0.00001$); $I^2 = 98\%$
Test for overall effect: $Z = 10.98$ ($p < 0.00001$)

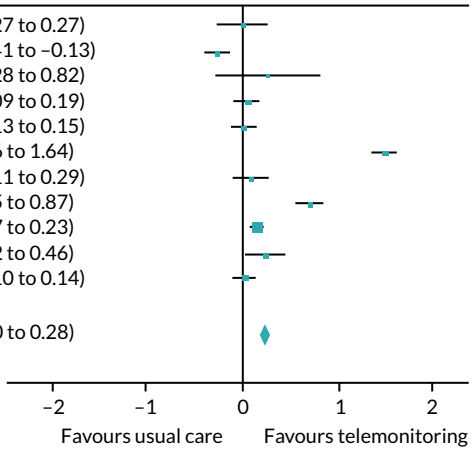


FIGURE 10 Forest plots to show RM vs. usual care on quality of life. (a) STS; and (b) TM. IV, inverse variance.

considerable (STS: $I^2 = 86\%$; TM: $I^2 = 98\%$). Using a random-effects model, the TM effect was found to no longer be significant (STS: SMD 0.24, 95% CI 0.1 to 0.37; TM: SMD 0.25, 95% CI −0.05 to 0.55; see *Table 19*).

Subgroup analyses for STS versus usual care showed significant results for a test for difference between groups for year of publication ($p = 0.003$) and average age ($p \leq 0.0001$); however, heterogeneity remained considerable for all groups. For all subgroup analyses of TM versus usual care, the test for group differences were significant; however, heterogeneity remained substantial for all pooled results; when it was reduced, it was for groups that pooled only one to three studies. Excluding studies with shorter follow-up durations and post hoc analyses using alternative quality-of-life surveys, imputed SE values or exclusion of studies with imputed data showed no difference to the main finding in the direction of effect, statistical significance or heterogeneity. For all analyses, see *Table 19*.

Length of stay, adherence, acceptability, heart failure knowledge and self-care

Data were reported for these secondary outcomes, but, similar to Inglis *et al.*,[73] data were limited and sufficiently varied in how they were measured and reported such that it was not possible to pool the evidence.

Of the 12 new included studies, two reported outcome data for length of stay in hospital: one for STS[147,148] and one for TM.[133] Neither study reported any difference between the RM and usual-care groups ($p = 0.76$ and $p = 0.21$, respectively). This was consistent with the findings in Inglis *et al.*,[73] in which the majority of studies for both STS and TM reported no significant difference in the length of stay for hospital admission.

Six new included studies, all TM versus usual care, reported adherence data.[129–132,134,138,139,145,146,149] Each study measured this differently, so comparison was not possible. For each study, compliance data were reported without comment, or for Kotooka *et al.*[131,132] and Smeets *et al.*[134] as 'sufficiently high' and 'excellent', respectively. All adherence rates for the eight studies, both STS and TM, in Inglis *et al.*[73] were reported as being > 55%.

Only two studies,[134,145,146] both newly included TM versus usual-care studies, considered acceptability (usability); both reported high satisfaction by patients for all aspects of the intervention. Furthermore, patients in Smeets *et al.*[134] 'experienced an extra sense of security'. Inglis *et al.*[73] stated narratively that six of the 41 studies reported satisfaction of > 75% with RM interventions and that two, which were videophone studies, had low satisfaction rates.

Dang *et al.*[145,146] and Wagenaar *et al.*[135,136] reported data for heart failure knowledge using the Dutch Heart Failure Knowledge Scale. Both these TM studies reported no difference between the TM and usual-care groups: Dang *et al.*[145,146] reported a non-significant mean difference at 3 months ($p = 0.09$) and Wagenaar *et al.*[135,136] reported no 'clear difference' at 12 months. Only one newly included study reported data on heart failure self-care: Wagenaar *et al.*[135,136] They reported no effect difference between the two groups (unadjusted and adjusted for self-care at baseline: $p = 0.082$ and $p = 0.184$, respectively). This varied from Inglis *et al.*,[73] in which five of the six studies evaluating heart failure knowledge and five studies evaluating heart failure self-care reported improvements in patients.

Discussion

Main findings

The evidence we pooled in this systematic review suggests that all-cause mortality and heart failure hospital admission rates reduced and that quality of life improved with the use of RM (both TM and STS). There was little difference between STS and TM in terms of the strength of effect or the degree of uncertainty surrounding it. Although there was some suggestion that RM may reduce all-cause

hospital admission, this was not statistically significant. It was not possible to pool data for length of stay, adherence, acceptability, heart failure knowledge or self-care.

For the outcomes of all-cause mortality and heart failure hospitalisation, the heterogeneity was low. Sensitivity analyses restricting the evidence to studies with longer follow-up durations suggest that the findings were not robust for TM, as, for both outcomes, it was no longer a statistically significant result. Heterogeneity was moderate for all-cause hospitalisation; this was not explained by subgroup analysis or meta-regression. The findings for quality of life should be viewed with caution as the heterogeneity was considerable, and testing of the robustness of the effect estimate by using a random-effects model resulted in the TM finding no longer being statistically significant.

Although it was not possible to pool data for secondary outcomes other than quality of life, it was possible to draw some narrative indications of the effectiveness of RM. There appeared to be no effect on the length of hospital stay for patients. In general, adherence and satisfaction with RM was good. In contrast to the Inglis *et al.*[73] review in 2015, the two more recent (2015–19) studies[135,136,145,146] reporting on heart failure knowledge and self-care found no improvement when using RM, compared with previously reported improvements.

Comparison with other reviews

This review is comparable with a number of previous reviews. The results are consistent with the findings of all four reviews published in 2018[125–128] in terms of the direction of effect, except for Carbo *et al.*,[126] who reported a trend towards the control group for all-cause hospital admission, although this was based on only five studies (compared with 24 studies in this review). Consistent with our review, all pooled results from previous systematic reviews are inconclusive for all-cause hospital admission. There is still variation between previous pooled results for all-cause mortality and heart failure-related hospital admission over whether or not the effect is statistically significant.

This systematic review was an update of the review by Inglis *et al.*,[73] and added 12 studies published since January 2015. The pooled results from this review are consistent with those of Inglis *et al.*,[73] reporting similar conclusions for the outcomes of all-cause mortality, all-cause hospital admission and heart failure-related hospital admission, and, for the majority, with marginally increased confidence in the findings. For this update, we were able to pool data for the secondary outcome of quality of life, which was reported only narratively in Inglis *et al.*[73]

Two previous systematic reviews have pooled data for quality of life. Our findings suggest a statistically significant improvement in quality of life using RM, is consistent with both Flodgren *et al.*[192] and Knox *et al.*[193]

Strengths and limitations

To our knowledge, this systematic review is the most comprehensive to date. There was no restriction on language or publication type in the study selection, although a study found in abstract form was included only if a full-text publication was available. Nevertheless, no cases of this were found in this update. However, it is possible that we missed relevant studies. Furthermore, we believe that this systematic review is the first to include evidence from the largest TM study to date.[129,130] Our ability to assess the methodological quality of studies was limited because of the number of studies assessed as being at unclear risk of bias in a domain; in particular, > 50% of studies were judged to have an unclear risk of bias for allocation concealment and blinding of outcome assessment. Further bias may be present as there was a strong suggestion of publication bias. We pooled data even in cases when there were few studies or high statistical heterogeneity, to give an overall indication of intervention effectiveness. We used reported average ages for each study to explore its association with the outcomes of interest, as done in the Inglis *et al.*[73] review that we used as the basis for this one. This is not recommended as it masks different population distributions found across the included studies. To have an adequate exploration of the impact that age has on these outcomes, individual patient data arising from these studies would be required.

Implication for clinical practice and research

In response to the 2010 NICE guideline,[70] there has been an increase in the number of studies investigating the clinical effectiveness of RM. This review includes 12 new studies published since 2015 and classifies 24 studies as ongoing. Seven studies are registered with www.clinicaltrials.gov.[194–200] One study has now presented their findings at conference,[194,201] one study is due to start in January 2021,[195] and five studies are completed or estimated to complete by August 2021, but have not yet published findings.[196–200] To consider whether or not sufficient evidence has been accumulated to date for STS studies, a simple sample size calculation (using 'power two proportions' in Stata) indicates that, to show an effect size as presented in this review (15% reduction in all-cause mortality), a study would need 10,120 patients to be sufficiently powered (baseline risk 11.4%,[161] two-sided alpha of 5% with a power of 80%). This review includes 9952 patients for this outcome. A similar calculation for TM studies indicates that, for an effect size of 18% reduction in all-cause mortality, a study would need 6544 patients to be sufficiently powered (baseline risk 12%[129,130]). Our review includes 7665 patients. The pooled evidence in this review indicates that, for the outcome of all-cause mortality, the threshold has now been reached for the comparison of TM with usual care. It is short of the threshold for STS versus usual care, although by < 500 patients. Therefore, there can be some level of confidence in the pooled results for all-cause mortality. As a result, we do not perceive the need for any new studies until the ongoing studies have reported their results, although this decision can be reviewed then in respect of other outcomes.

The 2018 NICE guideline[13] did not recommend the use of RM because of lack of evidence of effectiveness; our review would question this. Furthermore, although a reticence to recommend RM because of a lack of plateau in terms of technology advancement is understandable, we would argue that the pace of change and development of functionality is unlikely to stop, so recommendations should be made in spite of potential changes. However, it is true that RM interventions are complex and feature a number of interconnected factors. A key method to move these research findings into clinical practice would be to identify the beneficial components of the RM interventions that are associated with a clinical benefit to patients. Intervention synthesis[75] could be used to tease out the effect of components, such as different physiological measurements, frequency and duration of monitoring, incorporation of educational or motivational training, rural or urban settings, treatment protocols and severity of disease.

Conclusions

This review confirms the evidence base to date that all-cause mortality and heart failure hospital admission rates were reduced with the use of RM (both TM and STS). In addition, the review suggests that quality of life would be improved using RM; however, this result should be viewed with caution as the heterogeneity was considerable. The review does not provide evidence of an effect of RM on the rate of all-cause hospital admission.

Appendix 18 Diagnostic accuracy of point-of-care natriuretic peptide testing for chronic heart failure in ambulatory care: systematic review and meta-analysis

Taylor *et al.*[74] https://doi.org/10.1136/bmj.k1450

Appendix 19 Essential components in natriuretic peptide-guided management of heart failure: an intervention synthesis

Oke *et al.*[75] https://doi.org/10.1136/openhrt-2018-000826

Appendix 20 Estimation of variability of B-type natriuretic peptide and weight in the monitoring of chronic heart failure

Parts of this appendix have been reproduced from chapter 6 of Milena Kurtinecz's PhD thesis[66] with permission from Milena Kurtinecz (University of Oxford, 2021, personal communication).

Aim

The aim was to investigate the effects of factors that determine the BNP concentration and to estimate variability.

Proposed methodology

Secondary analyses of previously collected data from routinely collected data (CPRD) and pilot studies will be used to model BNP and weight to (1) identify biological variability and measurement error and determine coefficients of variation and (2) calculate rates of change by age, stratified by CHF severity.

Modifications

Evaluation of CPRD data identified that BNP measures are not commonly used. A small proportion (approximately 6%) of patients with CHF would have a BNP measure recorded, with most of these being a single measure. Instead, we obtained data from a RCT that collected repeated BNP measures on a small number of individuals with CHF. We determined that these would provide a better estimate for the variability of BNP in this population.

Objectives

- To estimate the within-subject short-term variability of BNP in non-diabetic, stable mild and moderate heart failure subjects (NYHA class II or III).
- To explore the impact of clinical, cardiac and other factors on the BNP variability.

Clinical factors: heart rate, systolic and diastolic blood pressure, and renal dysfunction.

Cardiac factors: LVEF, cardiac output, left ventricular end-diastolic and end-systolic volumes obtained from an echocardiography.

Other factors: age, sex and body mass index.

Methods

The objectives were addressed based on data from a phase 2 clinical trial in stable CHF patients in a post hoc analysis. This clinical trial is registered on www.clinicaltrials.gov with the clinical identifier number NCT01357850.[202]

The information provided in the register includes study description, condition/disease, study design, study start and completion dates, eligibility criteria, primary and secondary outcomes, participating sites and the primary publication.[203] Access to additional study documents, such as the statistical analysis plan, individual participant data sets, clinical study report, annotated case report forms, data specification, informed consent and study protocol, can be requested through www.clinicaltrials.gov.[202] A clinical trial setting provides the ideal opportunity to investigate the BNP variability because patients are assessed similarly and at the same time intervals throughout the study duration.[124]

Description of trial design

The study was a multicentre, randomised, placebo-controlled clinical trial that evaluated the safety of a new therapeutic agent in stable NYHA class II or III heart failure subjects. The investigational drug was in development for improved myocardial efficiency and increased exercise ability in heart failure patients. The clinical researchers and subjects were blinded to the study drug. The study design was a parallel group with four arms: placebo and three increasing dose levels of the new therapeutic agent. The 30 patients included in this appendix were not exposed to any dose of a new investigational medicine. Therefore, the BNP variability studied here cannot be attributed to such potential confounding. The study duration was 13 weeks, followed by an additional visit approximately 1 month after the study was completed. The clinical trial was initiated in September 2010 and ended in August 2012.

The BNP, cardiac output, LVEF, left ventricular end-diastolic volume, and left ventricular end-systolic volume was measured every 6 weeks, whereas the weight, heart rate, diastolic and systolic blood pressure measurements were collected weekly. The serum creatinine level was measured every other week, as described in *Table 20*.

Study participants

The clinical trial included clinically stable CHF patients on optimal therapies for at least 3 months before the baseline visit. The aetiology of CHF was ischaemic or non-ischaemic cardiomyopathy. Patients were in NYHA class II or III[204] for at least 6 months before enrolment in the study with a reduced LVEF (e.g. LVEF of $< 40\%$) at any time during the previous 24 months from the study start. Both males and females were between 21 and 75 years of age.

TABLE 20 Schedule of clinical measurements

	Week												
Measurement	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
BNP	✗						✗						✗
Cardiac output	✗						✗						✗
LVEF	✗						✗						✗
LVEDV	✗						✗						✗
LVESV	✗						✗						✗
Heart rate	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Blood pressure	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Weight	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Serum creatinine	✗		✗		✗		✗		✗		✗		✗

LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.
✗ indicates that the clinical variable was evaluated that week.

Patients with any of the following current or recent conditions were excluded: active ischaemia, diabetes mellitus, thyroid disease, genetic disorders of skeletal muscle, clinically significant pericardial diseases, renal dysfunction, history of coronary revascularisation, history of alcohol or drug abuse, history of deep-vein thrombosis or pancreatitis and other medical conditions with a life expectancy of < 1 year. Diabetes mellitus was assessed to be present based on a fasting glucose level of > 140 mg/dl or HbA_{1c} of > 7%. The renal dysfunction was determined based on an eGFR of < 40 ml/minute/1.73 m^2 at screening. Patients with a positive hepatitis B or C or human immunodeficiency virus test in the previous 3 months were excluded. Other reasons for exclusions at screening were calcitonin levels of > 100 pg/ml, triglycerides levels of > 850 mg/dl, resting low (< 85 mmHg) or high (> 170 mmHg) systolic blood pressure or high diastolic blood pressure (> 110 mmHg). Mentally incapacitated patients and pregnant women were also excluded from the study.

Outcomes

The primary outcome of this analysis was BNP. The unit of reporting was ng/l, which is the same as pg/ml. Although the assay type was not collected, all blood tests were processed at a central laboratory. The within-subject BNP variability was estimated over a 3-month period.

The between-subject BNP variability was described in subgroups of patients based on demographics, clinical characteristics, medical history and previous heart failure medication exposure. The changes in BNP levels up to 3 months were described.

Sample size and randomisation

The sample size of 30 participants includes only those that were randomised into the placebo arm of the trial and, therefore, did not receive any investigational medicine. The original study included a total of 82 participants with the other 50 participants allocated to one of three doses of the investigational medicine (with different allocation ratios). These 50 participants are not included in the present analysis.

Blinding

The clinical investigators and patients were blinded to the treatment received.

Statistical methods

The approach was exploratory and descriptive; therefore, no formal statistical hypothesis was tested. Summary statistics (e.g. *n*, mean, 95% CI for the mean, geometric mean, 95% CI for the geometric mean, standard deviation, SE, between-subject CV, median, range, interquartile range) were generated for BNP, weight, heart rate, serum creatinine level and systolic and diastolic blood pressure over time. A similar approach was adopted for the absolute changes from baseline and per cent changes from baseline in BNP over time.

Repeated-measures mixed models were employed to estimate the within-subject variability. Unlike the generalised linear models, mixed models incorporate random and fixed effects, allowing for correlations among measurements, as well as heterogeneous variance, while the normality assumption of the observations remains. Random factors were included to account for sources of variation, and their values were assumed to be a random sample from a population of interest whose values are normally and independently distributed. Consequently, some values could be higher or lower than the overall average effect. The model fit was evaluated by examining the marginal residuals, conditional residuals, covariance parameter diagnostics and influence diagnostics.

Using matrix notations, the general form of the mixed models is $Y = X\beta + Z\gamma + \varepsilon$,[205] where X is the known design matrix for the fixed effects, β is the vector of fixed effects, Z is the known design matrix for the random effects, γ is the unknown parameter vector of random effects and ε is the normally distributed random error. When variability is of interest, the focus is on the random part of the mixed models. Random intercept models with the intercept as a random effect and week as a fixed effect

were fitted, as well as random coefficient models, where the subject was a random effect and week was a fixed effect. The natural logarithm of the BNP baseline value was also modelled as a covariate.

B-type natriuretic peptide measurements taken over time in the same subject are expected to be correlated. Usually, the further apart the measurements, the lesser the correlation. The following covariance structures were considered: variance components, unstructured, compound symmetry, heterogeneous autoregressive and heterogeneous Toeplitz.

In the statistical analysis, BNP was transformed using natural logarithm because of the right skewness of its distribution, but the summary statistics are presented in the original scale.

The within-subject CV was calculated using the following formula:

$$\text{CVw}(\%) = 100 \times \sqrt[2]{\exp^{\sigma^2} - 1}, \quad (1)$$

where σ is the within-subject mean-square error from the mixed-model analysis of the BNP log-transformed levels.[205]

The reference change values (RCVs) were calculated using a log-normal approach based on the following derivations:[206–208]

$$\text{RCV}_{\text{positive}} = [\exp(1.96 \times 2^{1/2} \times \sigma) - 1] \times 1001. \quad (2)$$

$$\text{RCV}_{\text{negative}} = [\exp(-1.96 \times 2^{1/2} \times \sigma) - 1] \times 100. \quad (3)$$

The statistical analyses of weight, heart rate, serum creatinine level, and systolic and diastolic blood pressure were conducted on the original scale, without any data transformation. The within-subject CV was estimated as the square root of the residual variance from the intercept model divided by the overall mean. As each subject had several measurements taken, a subject's means were calculated for weight, heart rate, serum creatinine level, and systolic and diastolic blood pressure. In addition, the within-subject CV from a subject's mean was computed for each subject. An average within-subject CV was obtained for the clinical variable of interest.

The between-subject CV [CVb(%)] was calculated according to the following formula:

$$\text{CVb}(\%) = 100 \times \text{standard deviation/mean}. \quad (4)$$

Patients' characteristics were summarised using means and standard deviations for the continuous variables and counts and percentages for the categorical variables.

The BNP measurement for week 1 was considered as baseline. Changes in BNP over time were calculated as follows:

- Change in BNP to week 7 = $\text{BNP}_{\text{week7}} - \text{BNP}_{\text{baseline}}$.
- Change in BNP to week 13 = $\text{BNP}_{\text{week13}} - \text{BNP}_{\text{baseline}}$.
- Per cent change in BNP to week 7 (%) = $100 \times (\text{BNP}_{\text{week7}} - \text{BNP}_{\text{baseline}})/\text{BNP}_{\text{baseline}}$.
- Per cent change in BNP to week 13 (%) = $100 \times (\text{BNP}_{\text{week13}} - \text{BNP}_{\text{baseline}})/\text{BNP}_{\text{baseline}}$.

The body mass index was categorised into the following subgroups: underweight (< 18.5 kg/m^2), normal (18.5–24.99 kg/m^2), overweight (25–29.99 kg/m^2) and obese (≥ 30 kg/m^2). Kidney function was categorised into CKD stages G1–5 based on their GFR.[209] All statistical analyses were performed with SAS® version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Participants' characteristics

Thirty subjects were included in this analysis. One subject was withdrawn as a result of not entering the follow-up period and one subject had a missing BNP value at week 13. These two missing BNP values at week 13 were not imputed. Data for these two subjects were available for weeks 1 and 7. Therefore, 30 subjects were included in the analyses at week 1 and week 7, and 28 subjects were included in the analysis at week 13.

The study population was relatively young for a CHF group, with a mean age of 55.6 years. Most participants were male (70%) and of white ethnicity (86.7%), with almost half of the cohort categorised as obese (46.6%). The mean serum cholesterol level was 4.8 mmol/l, of which the average LDL cholesterol level was 2.7 mmol/l. The triglyceride levels were mostly in the normal upper range, with a mean of 1.7 mmol/l. Less than one-quarter (23.3%) were categorised as CKD stage G3, and approximately one-third (30%) had normal kidney function (CKD stage G1). The mean creatinine levels were 89.6 µmol/l, and urea levels were slightly higher than average. The study excluded diabetes patients, and the average blood glucose levels were slightly higher than normal. The platelets, calcium, potassium and sodium levels were normal. The patient characteristics of the cohort are presented in *Table 21*.

Approximately half (53.3%) of the participants reported hypertension as part of their medical history; however, a little over one-third (36.7%) of the cohort were hypertensive at baseline. The aetiology of the heart failure was mostly non-ischaemic. Eighty per cent of these CHF patients had left ventricular systolic dysfunction, and 56.7% had a history of arrhythmia. As expected, most of the patients had taken beta blockers, ACE inhibitors, diuretics and aldosterone antagonists. The cardiovascular medical history and past exposure to the cardiovascular medication are summarised in *Table 22*.

TABLE 21 Demographics and clinical characteristics at baseline

Patient characteristics	Summary statistics
Age (years), mean (SD)	55.6 (9.6)
0–44, *n* (%)	4 (13.3)
45–54, *n* (%)	9 (30)
55–64, *n* (%)	13 (43.4)
65–74, *n* (%)	4 (13.3)
Female, *n* (%)	9 (30)
Male, *n* (%)	21 (70)
Body mass index (kg/m^2), mean (SD)	31.3 (6.4)
Normal weight, *n* (%)	5 (16.7)
Overweight, *n* (%)	11 (36.7)
Obese, *n* (%)	14 (46.6)
Ethnicity, *n* (%)	
African/American	3 (10)
Native Hawaiian/Pacific Islander	1 (33)
White	26 (86.7)
Cholesterol (mmol/l), mean (SD)	4.8 (1.1)
LDL cholesterol (mmol/l), mean (SD)	2.7 (1)

continued

TABLE 21 Demographics and clinical characteristics at baseline (*continued*)

Patient characteristics	Summary statistics
Triglycerides (mmol/l), mean (SD)	1.7 (0.8)
GFR (ml/m/1.73 m^2), mean (SD)	77.3 (21.8)
CKD stage, *n* (%)	
G1	9 (30)
G2	14 (46.7)
G3	7 (23.3)
Creatinine (µmol/l), mean (SD)	89.6 (22.8)
Urea (mmol/l), mean (SD)	7.2 (2.3)
HbA_{1c} (%), mean (SD)	5.8 (0.4)
Platelet (GI/l), mean (SD)	221.7 (50.2)
Calcium (mmol/l), mean (SD)	2.4 (0.1)
Potassium (mmol/l), mean (SD)	4.5 (0.4)
Sodium (mmol/l), mean (SD)	139.1 (2.5)

SD, standard deviation.

TABLE 22 Cardiovascular medical history and medication exposure

Cardiovascular medical history	Participants (*N* = 30), *n* (%)
Angina	4 (13.3)
Arrhythmia	17 (56.7)
Hypertension	16 (53.3)
Ischaemic cardiomyopathy	11 (36.7)
Non-ischaemic cardiomyopathy	19 (63.3)
Left ventricular systolic dysfunction	24 (80)
Left ventricular diastolic dysfunction	8 (26.7)
Myocardial infarction	5 (16.7)
Valvular heart disease	7 (23.3)
Cardiovascular medication exposure history	
ACE inhibitor	22 (73.3)
Aldosterone antagonist	20 (66.7)
Angiotensin II antagonist	8 (26.7)
Beta blocker	27 (90)
Diuretics	21 (70)

The average weight was close to 95 kg. On average, the mean heart rate was normal, centred around 70 beats per minute. Although a little over half of the cohort had reported a diagnosis of hypertension in the past, most of the subjects were exposed to blood pressure-lowering medication before entering the study. During the study period, the blood pressure for the cohort was normal, on average. The mean diastolic blood pressure for the cohort was < 70 mmHg during most of the weeks. On average, the serum creatinine level was in the low 90s (of μmol/l), with a standard deviation varying from 21.6 μmol/l (week 13) to 23.9 μmol/l (week 3).

Consistent with a stable, relatively young, CHF population, there were relatively few heart failure medication changes over the course of the clinical trial. One patient was prescribed losartan (100 mg once daily) on the 10th day into the trial and then added amlodipine (5 mg) on the 29th day into the clinical trial to control his hypertension. Another patient had a dose increase in carvedilol [i.e. from 3.125 mg bis in die (b.i.d.) on day 76 to 6.25 mg b.i.d. on day 77]. One patient had a dose reduction in lisinopril (i.e. from 30 mg once daily starting on day 6 to 20 mg once daily beginning on day 29) while taking furosemide (30 mg b.i.d.). Another patient was given an ACE inhibitor starting on day 45 (i.e. lisinopril, 2.5 mg once daily), adding a diuretic (i.e. furosemide, 40 mg once daily) and a potassium replacement on day 49. Another patient had a decrease in diuretics during the trial (i.e. furosemide, 40 mg b.i.d. from day 49 to 40 mg once daily starting from day 52).

B-type natriuretic peptide measures

The baseline BNP levels ranged from 5 ng/l to 605 ng/l at baseline. The BNP levels were < 100 ng/l for 60% of the patients ($n = 18$) and were between 100 and 199.9 ng/l for eight subjects. There were only four placebo subjects with a baseline BNP value of > 200 ng/l, and, for two of them, such values were > 400 ng/l at baseline. Counts and frequency of patients based on their BNP levels at baseline are presented in *Table 23*.

The means and standard deviations over time for weight, heart rate, systolic and diastolic blood pressure, serum creatinine level and BNP are presented in *Table 24*.

Between-subject B-type natriuretic peptide variability

The ranges of BNP values were 5 ng/l to 605 ng/l, 6 ng/l to 601 ng/l and 3 ng/l to 721 ng/l at week 1, week 7 and week 13, respectively. Two subjects did not have BNP measurements at week 13 either because of withdrawal or missing values. The individual BNP profiles (*Figure 11*) reveal no trends of BNP levels over time. One subject had BNP values of > 600 ng/l at all time points: 605 ng/ml at week 1, 601 ng/ml at week 7 and 721 ng/l at week 13, from the study start. This subject was a 50-year-old white male, weighing 84.7 kg. His medical history included left ventricular systolic dysfunction and dilated cardiomyopathy, as well as pulmonary embolic disease, which explains the high BNP values. Prior medication exposure included ramipril (5 mg once daily), bisoprolol (1.25 mg once daily), spironolactone (25 mg once daily), furosemide (80 mg once daily) and warfarin (7 mg once daily). Current medication during the study period included furosemide (40 mg once daily) and erythromycin (500 mg) taken during the seventh week in the trial for an upper tract respiratory infection.

TABLE 23 Baseline BNP categories

BNP category (ng/l)	Counts	Per cent of patients
< 100	18	60
100–199.9	8	26.6
200–400	2	6.7
> 400	2	6.7
Total	30	100

TABLE 24 Means and standard deviations for weight, vital signs and creatinine levels by week

Week	Weight (kg)	Heart rate (bpm)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Creatinine[a] (μmol/l)	BNP[b] (ng/l)
1	93.4 ± 23.2	71.4 ± 12.7	114.8 ± 14.6	69 ± 8.4	93.9 ± 22.8	114.8 ± 136.8
2	93.6 ± 23	68.9 ± 10.1	116.2 ± 21.9	66.9 ± 10.6	–	–
3	94.7 ± 23.4	67.9 ± 10.8	115.6 ± 17.2	68.5 ± 8.1	90.2 ± 23.8	–
4	95.1 ± 22.8	69.1 ± 12.8	115.6 ± 16.7	69.7 ± 8.4	–	–
5	94 ± 23.1	71.9 ± 11.4	115.6 ± 17.1	69.9 ± 8.8	94.1 ± 23.5	–
6	94.3 ± 23.6	69.7 ± 13.6	112.5 ± 17.3	66.7 ± 7.6	–	–
7	94 ± 23	66.8 ± 11.2	115.2 ± 15.6	67.7 ± 9	91.1 ± 23.4	112.9 ± 121.6
8	93.7 ± 23.8	66.8 ± 10.2	112.7 ± 17	67.9 ± 10.3	–	–
9	95.5 ± 22.9	68.9 ± 11.2	114.6 ± 18.4	68.2 ± 10.9	90.1 ± 20.9	–
10	94.8 ± 24	69.2 ± 10.7	114.2 ± 16.5	68.6 ± 9.1	–	–
11	94.5 ± 23.7	68.2 ± 11.8	111 ± 18.7	68.5 ± 11.6	92.7 ± 22.8	–
12	94.3 ± 23.8	69.4 ± 10.6	113.7 ± 17.1	68.3 ± 9.1	–	–
13	93.8 ± 24	69.6 ± 11.7	115.6 ± 16.7	70.7 ± 10.8	92.9 ± 21.6	103.5 ± 141.6

bpm, beats per minute.
a Serum creatinine level was measured at weeks 1, 3, 5, 7, 9, 11 and 13.
b BNP level was measured at weeks 1, 7 and 13.

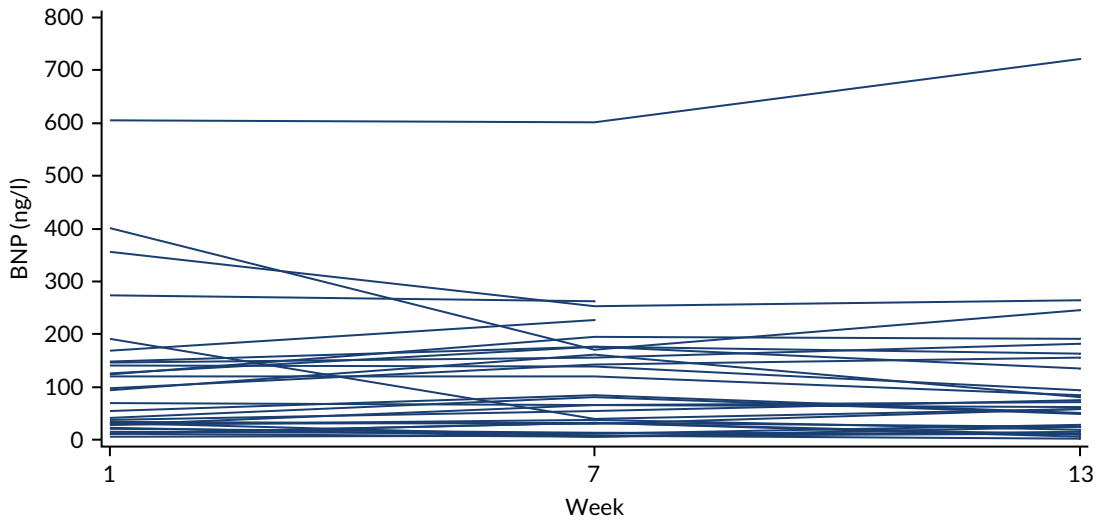


FIGURE 11 Individual profiles of BNP throughout the clinical trial duration.

As illustrated in *Figure 12*, average BNP levels decreased over time. The mean BNP levels were 114.8 ng/l at week 1, 112.9 ng/l at week 7 and 103.5 ng/l at week 13. Compared with baseline, between-patient BNP variation decreases in week 7, and then increases at week 13. The between-subject CV was 119.2%, 107.7% and 136.8% at weeks 1, 7 and 13, respectively. This shows the extent of BNP variability about the mean of the population. Summary statistics for BNP values are presented in *Table 25*.

On average, there were no significant changes in BNP from baseline to week 7 or week 13. All summary statistics generated for the change from baseline in BNP are presented in *Table 26*, and in *Table 27* for the per cent changes from baseline.

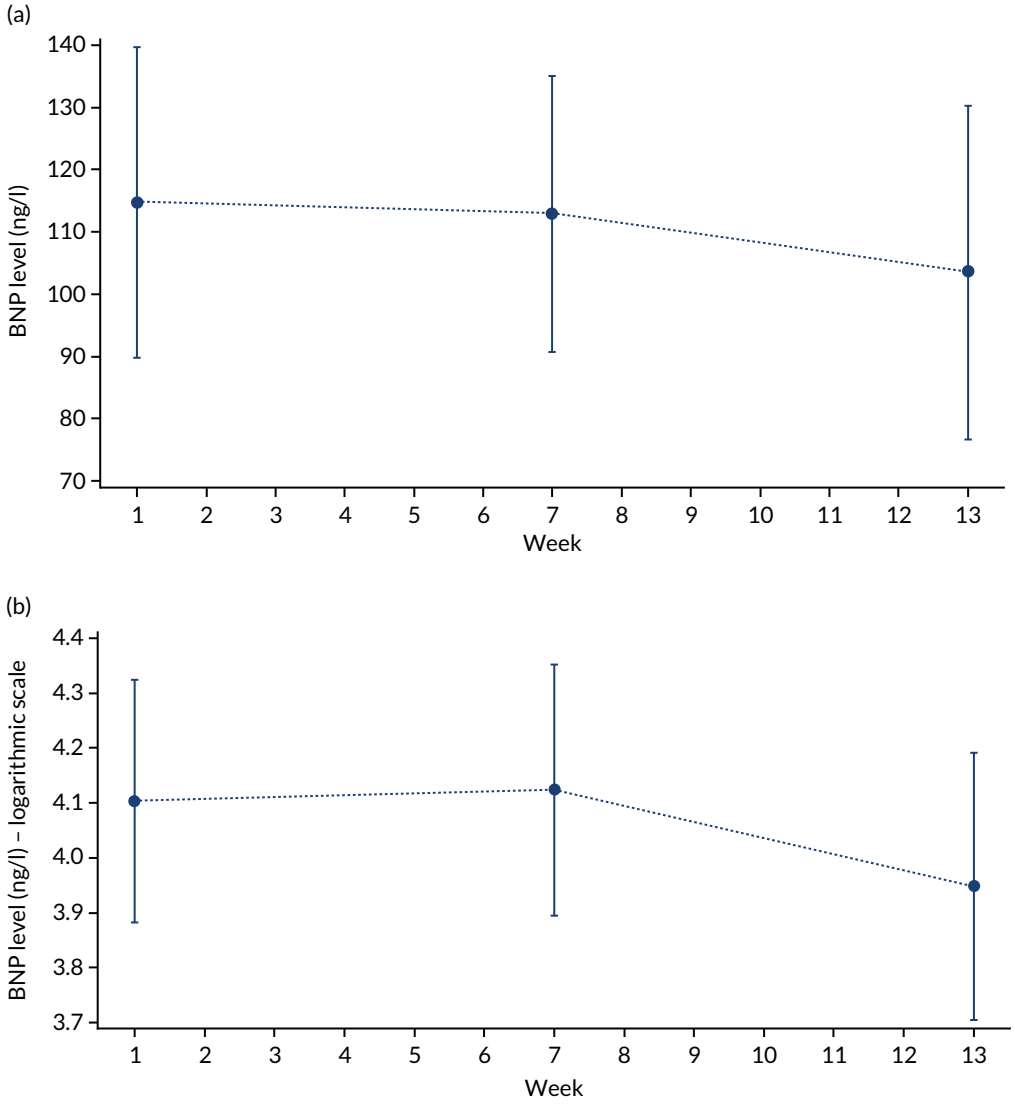


FIGURE 12 Mean/SE plot for BNP levels over time. (a) Original; and (b) logarithmic scales.

TABLE 25 Measures of location and variability for BNP (ng/l) values over time

Summary measure	Week 1	Week 7	Week 13
Number of participants included	30	30	28
Arithmetic mean (95% CI)	114.8 (63.7 to 165.8)	112.9 (67.5 to 158.3)	103.5 (48.6 to 158.4)
Standard deviation	136.8	121.6	141.6
SE	25	22.2	26.8
Geometric mean (95% CI)	60.3 (40.4 to 99.5)	60.3 (40.4 to 99.5)	49.4 (30 to 81.5)
Standard deviation on natural logarithmic scale	1.2	1.3	1.3
Between-subject CV (CV_b%)	119.2%	107.7%	136.8%
Median	62	73	61
Minimum, maximum	5, 605	6, 601	3, 721
Lower quartile, upper quartile (Q1, Q3)	28, 146	32, 170	21.5, 145.5
Interquartile range (Q3 – Q1)	118	138	124

Note
Unless otherwise noted (standard deviation on natural logarithmic scale), the data were reported in the original scale.

TABLE 26 Changes from baseline over time in BNP (ng/l)

Summary measure	Change from baseline to week 7	Change from baseline to week 13
Number of participants included	30	28
Arithmetic mean (95% CI)	−1.8 (−25 to 21.3)	−3.7 (−25.1 to 17.7)
Standard deviation	62	55.2
SE	11.3	10.4
Geometric mean (95% CI)	1 (0.8 to 1.3)	0.9 (0.7 to 1.1)
Standard deviation on natural logarithmic scale	0.7	0.5
CV (CV_b%)	−3381	−1500
Median (range)	3 (302)	−3 (271)
Minimum, maximum	−231, 71	−155, 116
Lower quartile, upper quartile (Q1, Q3)	−5, 30	−12.5, 30
Interquartile range (Q3–Q1)	35	42.5

Notes
Change from baseline to week 7 = week 7 − baseline (week 1). Change from baseline to week 13 = week 13 − baseline (week 1). Unless otherwise noted (e.g. standard deviation on natural logarithmic scale), the data were reported in the original scale.

TABLE 27 Per cent changes from baseline in BNP (ng/l) over time

Summary measure	Per cent change from baseline to week 7	Per cent change from baseline to week 13
Number of participants included	30	28
Mean	21.5%	7%
Standard deviation	66.8%	56.2%
Median (range)	8.1% (270%)	−11% (196.9%)
Minimum, maximum	−79.1%, 190.9%	−69.6%, 127%

Note
Data reported in the original scale (ng/l).

Between-subject B-type natriuretic peptide variability in subgroups of patients

Heart failure is a heterogeneous disease. The between-subject variability was generated by subgroups defined by age, sex, body mass, ethnicity and clinical characteristics. The BNP between-subject CV varied over time and was higher for those aged < 55 years. The cohort included only five subjects with a normal body mass index. Therefore, in the present appendix, weight was categorised as normal/overweight versus obese to allow meaningful comparisons between subgroups. For both normal/overweight and obese subgroups, the BNP between-subject CVs decreased from baseline to week 7 and then peaked at week 13. The between-subject CV was lower among obese subjects than among normal or overweight subjects (*Table 28*).

The BNP between-subject CVs for various subgroups defined by a history of hypertension, arrhythmia and ischaemic and non-ischaemic cardiomyopathy are presented in *Table 29*. The between-subject variability in BNP was also described in subgroups of subjects defined by prior exposure to medication

TABLE 28 The between-subject CV of BNP by age subgroups

Parameter	Subgroup	CV_b (%); number of participants (*n*)		
		Week 1	Week 7	Week 13
Age (years)	< 55	149.3; *n* = 13	145; *n* = 13	169.9; *n* = 13
	≥ 55	100; *n* = 17	74.2; *n* = 17	88.4; *n* = 15
Body mass index	Normal/overweight	129.7; *n* = 16	112.6; *n* = 16	133.5; *n* = 16
	Obese	104.9; *n* = 14	97.6; *n* = 14	120.4; *n* = 12

TABLE 29 The between-subject CV of BNP by cardiovascular medical history and cardiovascular medication exposure

Subgroup	CV_b (%); number of participants (*n*)		
	Week 1	Week 7	Week 13
History of hypertension	101.9; *n* = 16	83.6; *n* = 16	97.5; *n* = 14
History of arrhythmia	94.1; *n* = 17	63; *n* = 17	73.5; *n* = 16
History of ischaemic cardiomyopathy	102; *n* = 11	71; *n* = 11	75.6; *n* = 10
History of non-ischaemic cardiomyopathy	124.4; *n* = 19	119.7; *n* = 19	154.8; *n* = 19
Prior beta blocker	122.5; *n* = 27	111.5; *n* = 27	147; *n* = 25
Prior ACE inhibitor	130; *n* = 22	125.9; *n* = 22	169.5; *n* = 20
Prior aldosterone antagonist	134.8; *n* = 20	126.4; *n* = 20	165.8; *n* = 18
Prior angiotensin II antagonist	92.5; *n* = 8	63.6; *n* = 8	71.5; *n* = 8
Prior diuretic	121.7; *n* = 21	117.6; *n* = 21	148.4; *n* = 21

commonly prescribed to heart failure patients: beta blockers (e.g. carvedilol, carvedilol phosphate, metoprolol, metoprolol succinate, nebivolol hydrochloride and bisoprolol), ACE inhibitors (e.g. captopril, lisinopril, enalapril, ramipril or quinapril), aldosterone antagonists (e.g. spironolactone or eplerenone), angiotensin II antagonists (e.g. losartan, losartan potassium, valsartan, candesartan or candesartan cilexetil) and diuretics (e.g. torasemide, furosemide, metolazone, hydrochlorothiazide or bumetanide). As, often, heart failure patients have multiple comorbidities and are prescribed multiple medications, the table should be read in the context of each line without comparing the subgroups or multiple lines at a time. The between-subject CV was high in those with a history of non-ischaemic cardiomyopathy and those previously exposed to aldosterone antagonists, ACE inhibitors, beta blockers or diuretics.

Within-subject B-type natriuretic peptide variability

Two random intercept models were fitted to the log-transformed BNP repeated measures, one including baseline BNP and one excluding this measure. Both models showed the same effect on the average increase in BNP per week; therefore, the random intercept model with the BNP baseline as a covariate was dropped to avoid model overparameterisation. This model included week as a fixed effect in addition to the random intercept, and was fitted using restricted maximum likelihood estimation for variance components. Most of the subjects had three BNP measurements over time, accounting for the 88 observations used in the model. The estimated BNP within-subject CV was 46%, with the rest of the model estimates reported in *Tables 30* and *31*. The average BNP value at baseline on the naturally logarithmic scale was 4.1267, corresponding to a BNP geometric mean of 62 ng/l, with no evidence of an average increase in BNP per week.

TABLE 30 Model estimates: fixed effect components

Covariance parameter	Estimate
Intercept	1.3802
Residual	0.1909
Within-subject CV	45.86%
RCV_+ (upwards)	242%
RCV_- (downwards)	−70.7%

TABLE 31 Model estimates: random effect components

Effect	Estimate	SE	Degrees of freedom	*t*-value	Pr > |*t*|
Intercept	4.1267	0.2291	29	18.01	0.0001
Week	−0.0055	0.0096	57	−0.57	0.5704

As suggested by the BNP individual profiles over time (see *Figure 11*), the results of the random intercept model showed no evidence of progression or deterioration over time. Sensitivity analyses were conducted when excluding the two subjects with missing BNP values at week 13. The results were robust to transformation and differences in model selection.

Within-subject variability for BNP was much higher than the variability for other clinical variables often measured in primary care practice, such as weight, heart rate, blood pressure or serum creatinine. The estimated within-subject CVs are displayed in *Table 32*.

Discussion

We used data from the placebo arm of a clinical trial providing repeated measurements taken over time to estimate the between- and within-subject variability for BNP. The study participants were stable CHF patients of NYHA class II or III. Ninety per cent of the cohort had been exposed to cardiovascular drugs before the baseline; therefore, their NP levels were expected to be similarly affected. This could be one of the reasons why BNP was stable, and few medications were changed over time.

TABLE 32 Within-subject CV for weight, heart rate, blood pressure and serum creatinine level

Group of patients	*n*	Estimated CV_w (%) from mixed models[a]	Average CV_w (%)[b]
Weight	30	1.2	1.1
Heart rate	30	10.3	9.6
Systolic blood pressure	30	9.7	8.7
Diastolic blood pressure	30	10.7	10.3
Serum creatinine level			
All	30	8.9	7.3
Females	9	10.7	8.2
Males	21	8.1	6.9

a Estimated from the random intercept mixed model.
b Derived as the average of CVw(%) = 100 × within-subject standard deviation/subject's mean.

The BNP within-subject variability over a 3-month period was 46%, with large RCVs. The results suggest that monitoring over 3 months is unlikely to detect true BNP change against background noise in this small, chronically stable, heart failure population. For reference, a change in BNP would have been detected as statistically significant if there had been an increase in BNP of at least 235% or a decrease of at least 70.2% between two consecutive visits.

Troughton and Richards[210] reported variability of 30% between serial measurements in NT-proBNP. Meijers *et al.*[211] reported log-normal RCVs upwards and downwards of 104.9 and −40.1, respectively, in 83 heart failure patients over a 6-week period. The Study Group on Biomarkers in Cardiology of the ESC acknowledged intraindividual biological variability of between 30% and 50% for all NPs.[212] CHF patients are typically treated using several drugs to deal with their condition and various existing comorbidities. Drug–drug interactions and poor adherence are likely to affect increasing within-subject variability.

Limitations

The main limitations of this analysis are the small sample size and short duration of follow-up. The placebo cohort included only 30 subjects. Therefore, the CIs were wide, suggesting high imprecision. Similarly, subgroup analyses were affected by the small sample size. The younger age and lower body mass index subgroups included few subjects, but this was not surprising given the heart failure epidemiology. Laboratory and cardiac imaging parameters were summarised on a continuous scale, thus avoiding subgrouping whenever possible. Although 30% of the subjects were females, given the small sample size, this corresponded to only nine women. The 3-month study duration was relatively short: about 30–40% of CHF patients die within the first year of being diagnosed with heart failure.[52,53]

The results are not generalisable to people with diabetes because the study did not include patients with type 2 diabetes mellitus. BNP values are higher in diabetic CHF patients.[213] The results are not generalisable to patients with a history of renal failure, characterised by a GFR of < 40 ml/minute/1.73 m^2.

The BNP reference ranges and analytical performance depend on the assay being used to measure them.[214] The analytical imprecision of commercially available BNP assays varies from 3.1 to 16.7.[214] The NT-proBNP intra-assay precision was 5.4% for the IMMULITE® 2000 assay (Siemens Healthineers AG, Erlangen, Germany).[215] The 30 subjects included in this appendix were enrolled at 11 different sites. Unfortunately, the BNP assay was not collected; therefore, the assay imprecision could not be evaluated. The extent of this measurement bias is unknown in this study.

The aetiology of the CHF for all participants was cardiomyopathy of an ischaemic or non-ischaemic origin. However, the CHF duration was not available, but, given that this is a trial, it is unlikely that considerable differences existed between participants. The study included CHF patients with NYHA class II or III at screening; however, this symptomatic classification was not collected throughout the clinical trial. Thus, a potential change in NYHA class could not be assessed.

Implications for research and clinical practice

Owing to the small sample size of only 30 research subjects, the results of this study need to be replicated in larger cohorts of CHF patients, potentially of varying degrees of severity. Clinical trial data from CHF patients being monitored for > 3 months may provide additional insight.

The high within-subject variability of the BNP levels poses severe limitations when monitoring CHF patients in the primary care setting. In stable chronic, relatively young, heart failure patients, monitoring BNP over a 3-month period is of limited value. Although other clinical biomarkers (e.g. heart rate, weight, blood pressure and serum creatinine level) have a much lower within-subject

variability in this population, only BNP has been identified as having a clear prognostic association with severity (e.g. all-cause mortality) among patients with CHF. Relevant to this, weight profiles in this study were mostly flat during the follow-up period. The within-subject CV of weight was 1.2%. The slight weekly fluctuations in weight during the study period did not appear to be associated with high BNP values.

Conclusion

The BNP within-subject variability over a 3-month period was 46%. The BNP upwards and downwards values for the log-normal RCVs were 235% and –70.2%, respectively.

Appendix 21 Observational feasibility study of point-of-care NT-proBNP monitoring in patients with heart failure in primary care

Authors: Susannah Fleming, Clare J Taylor, Richard Stevens and Clare Bankhead.

Introduction

Heart failure is a chronic disease, which can result in significant morbidity and mortality. NP levels are currently used as part of the diagnostic pathway in heart failure, and have been shown to correlate with poor prognosis.[216] Patients with heart failure receive much of their care in the community, either in primary care or through specialist community heart failure nurses, and are referred to secondary or tertiary care as required if they experience acute illness or deterioration.

It has been postulated that routine monitoring of NP could assist in improving the care of patients with heart failure in the community.[216] Recent advances in technology provide the possibility of POC NP testing, but there is currently no evidence to support the use of such devices as part of routine care of patients with heart failure in primary care.

Both BNP and NT-proBNP appear to have similar predictive value in heart failure.[216,217] However, NT-proBNP appears to have less biological variation than BNP in patients with heart failure.[211,218–222]

The primary aim of this study was to determine the variability in NP measurements made using POC NP technology in patients with heart failure in primary care settings, including both between- and within-person variability.

Methods

This is a feasibility study, comprising an observational cohort study of POC NP measurement. A previous horizon scan of POC NP devices suitable for use in the diagnosis of heart failure in primary care identified two potential POC NT-proBNP devices.[217] Of these, we chose to use the Roche Cobas h 232 device (Roche Diagnostics, Switzerland), as this was the device for which the most evidence is available, and is also the only one for which a UK distributor could be identified. It also carries a Conformité Européenne (CE) mark and is currently marketed in the UK as a POC assessment of NT-proBNP for diagnosis of heart failure.

We recruited patients from three GP practices in Oxfordshire. Prospective patients were identified by searching the practice register for adults with a recorded diagnosis of heart failure, and were checked by a clinician against the inclusion and exclusion criteria for the study (*Table 33*). Eligible patients were invited to take part by post or direct invitation by a member of the practice team. Recruitment to the study took place from 20 February 2018 to 28 March 2018, with follow-up to 29 March 2019.

Participants attended three scheduled visits at 0, 6 and 12 months from baseline. Visits were carried out at the participant's usual GP surgery, with a practice nurse trained in the use of the POC device. At all three visits, three venous blood samples were taken: one for POC NT-proBNP measurement and two to be sent to the local laboratory for NT-proBNP and renal function testing.

TABLE 33 Inclusion and exclusion criteria for participants in the NP POC feasibility study

Inclusion criteria	Exclusion criteria
• Willing and able to give informed consent • Male or female • Aged ≥ 18 years • Confirmed diagnosis of heart failure made by cardiologist and/or echocardiography • Currently managed in primary care • Clinician willing to offer routine NP POC monitoring	• Terminally ill or receiving palliative care for a condition other than heart failure at time of recruitment

We also requested that, where possible, additional POC NT-proBNP measurements should be taken when study participants attended the practice outside their scheduled visits for any reason related to their heart failure. However, owing to the potential additional waiting time that this may cause for patients, we did not require that these measurements must be taken.

Statistics and sample size

The sample size for this study was chosen based on practical judgement rather than a formal sample size calculation, as this is a feasibility study. We judged that a sample of 30 patients would be sufficient to test our primary outcome measure, and recruited three practices based on a predicted recruitment of 10 patients per practice.

Where results from the POC device were reported at the end of the range, we analysed them using the value closest to the range of the device (i.e. values reported as < 60 pg/ml were analysed as 59 pg/ml and those reported as > 9000 pg/ml were analysed as 9001 pg/ml).

Within-person variability was calculated as the mean of within-person standard deviations, and between-person variability was calculated as the standard deviation of within-person means.

Results

Descriptive statistics of population

We recruited 27 participants from three GP practices to take part in the study. *Figure 13* shows participant flow through the study. The median follow-up time was 366 days, with a maximum of 396 days, and the total study follow-up time was 24.5 person-years.

Three participants discontinued participation during the study, two of whom only attended visit 1, and one participant attended both visit 1 and visit 2. Two participants discontinued because of changes in circumstances and one participant died during the course of the study.

Two participants did not attend visit 2 during the study but were not discontinued as they attended for visit 3. POC NT-proBNP measurements were successfully obtained at all visits attended by participants. No patient in the study had POC NT-proBNP measured at a routine GP appointment.

Table 34 summarises the baseline characteristics of the study population. The most common comorbidities reported at baseline were hypertension (15 participants, 55.6%), CKD (10 participants, 37.0%), arthritis (nine participants, 33.3%), and cancer (six participants, 22.2%).

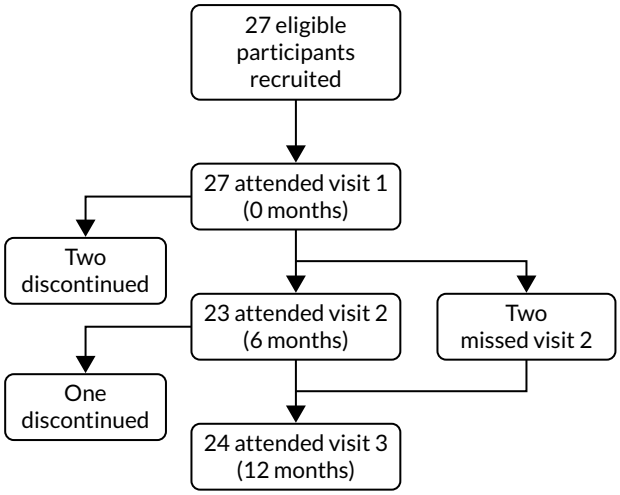


FIGURE 13 Flow of participants in the observational study of POC NT-proBNP. Patients noted as discontinued did not attend any further visits. The two participants who missed visit 2 but were not discontinued continued to attend at visit 3.

TABLE 34 Baseline characteristics of participants in the observational study of POC NT-proBNP ($n = 27$)

Characteristic	Summary, *n* (%)
Age in years (mean, SD)	77.6 (9.1)
Sex	
Male	10 (37.0)
Female	17 (63.0)
Ethnicity	
White British	25 (92.6)
White other	1 (3.7)
Indian	1 (3.7)
Type of heart failure	
Heart failure with preserved ejection fraction	10 (37.0)
Heart failure with reduced ejection fraction	13 (48.1)
Unknown	4 (14.8)
Baseline NYHA functional classification	
Class I	8 (29.6)
Class II	14 (51.9)
Class III	4 (14.8)
Class IV	1 (3.7)

Primary analysis

Within-person variability was calculated using data from 25 participants. The two participants who were discontinued after visit 1 had only one POC measurement, and so could not contribute to this analysis. Within-person variability in POC NT-proBNP over 12 months was 881 pg/ml (95% CI 380 to 1382 pg/ml). Between-person variability was calculated using data from all 27 participants. Between-person variability in POC NT-proBNP over 12 months was 1972 pg/ml (95% CI 1525 to 2791 pg/ml).

Discussion

Principal findings

We found that it was feasible to carry out POC NT-proBNP testing in primary care, with testing successfully carried out in 100% of planned study visits. However, no tests were carried out during routine primary care visits by the study participants.

Between-person variability in POC NT-proBNP was around twice as large as within-person variability over a 12-month period. This would indicate that deviations from individual set points for NT-proBNP are likely to be more helpful than population-level thresholds when considering a monitoring strategy.

Strengths and weaknesses

As this is a feasibility study, the main weakness is the limited sample size. However, despite this, we have been able to clearly determine that it is possible to carry out POC NT-proBNP testing in primary care. However, this is limited to the situation of a pre-booked appointment with a clinician trained and prepared to use the POC device, and with sufficient time within the appointment to carry out venepuncture and wait for the POC device to provide a result. In this study, we did not mandate attempting to carry out POC testing during routine or unplanned appointments, or reporting why it was not carried out, so we do not have evidence of the barriers that prevented testing.

Comparison to other studies

Most previous studies assessing POC BNP or NT-proBNP have done so in secondary care. One previous study in Belgium[223] assessed the practicality and accuracy of POC NT-proBNP for diagnosis of heart failure in primary care, using the same device as was used in this study. They found that GPs were able to incorporate the device into routine practice and showed high levels of acceptability from the GPs. A notable difference between the two studies is that all GPs at the participating practices in the study by Hex *et al.*[223] were trained to use the POC device, whereas in our study, only one or two practice nurses were trained to do so. This may have had implications for the practicality of carrying out unplanned POC tests.

Implications for clinicians or policy-makers

This study shows that it is feasible to monitor NT-proBNP in patients with heart failure using POC testing in primary care. This has important implications for the implementation of guideline recommendations that include NP monitoring following recent hospitalisation to prevent readmission. The lack of POC testing in routine appointments seen in our study is likely to reflect the current pressures in primary care. If unscheduled NP testing is to be successfully used, other factors such as sufficient time, training and staff available to carry out testing may need to be considered.

Unanswered questions and plans for future research

Further secondary analysis of the data gathered in this study should allow us to assess the potential impact that POC NT-proBNP testing in primary care has on clinical decision-making and to further investigate how the POC device fitted into the primary care workflow. Further research is needed to identify if and how this type of POC testing could be incorporated into routine primary care and to assess the potential benefit of monitoring of NT-proBNP in patients with heart failure who are managed in primary care.

Further research to characterise the short-term variability of POC NT-proBNP (e.g. within 1 day or 1 week) would also be valuable, as would assessments of whether or not accuracy and variability was dependent on operator skill level (e.g. nurse, health-care assistant or lab technician).

Appendix 22 A systematic review of economic models of chronic heart failure and economic issues of monitoring chronic heart failure

Introduction

The prevalence of CHF is rising[47] and there is a growing interest in efforts to optimise its management in primary care. Economic evaluations are required to assess competing strategies and inform policy decisions on the efficient use of resources. These require long-term CHF models. We aimed to review available models of CHF that were potentially suitable to inform such assessments with a focus on the model structure and data used. We discuss limitations of available CHF economic models to assess CHF interventions in a primary care setting and make recommendations for future research.

Methods

An earlier published systematic literature review of decision-analytic models to project health outcomes and costs in patients with heart failure by Goehler *et al.*[77] was updated. Unlike Goehler *et al.*,[77] who considered all models regardless of care setting for CHF, we explicitly focused on models that could be used to assess management and treatment strategies for CHF in a primary care setting. Briefly, the search strategy in Goehler *et al.*[77] was implemented in MEDLINE and EMBASE, and was used to search for eligible publications from 1 June 2010 to 31 August 2018. The study inclusion criteria required the study to include a mathematical model that evaluated costs and health effects of health technologies. Studies that were short-term economic evaluations alongside clinical trials were excluded, as were studies where a model was used only to illustrate a methodological concept or was a non-UK adaptation of a study already included in the review model. Only full-text English-language studies were included. Since the review focused on methodological approaches, a formal protocol registration was not sought.

Studies were reviewed and data were extracted using a set of six broad questions:

1. What were the study characteristics?
2. How was the model structured?
3. How was disease progression modelled?
4. How was the treatment effect of the intervention modelled?
5. Did the model take into account patient characteristics?
6. What data sources were used to inform model parameters (i.e. for the disease end points, quality of life and costs)?

The information to answer these questions were independently extracted into a predefined spreadsheet from each study by either CS or BM with queries resolved by discussion (CS and BM). As in Goehler *et al.*,[77] we did not formally assess the quality of the methods used or studies from which data were sourced as the aim was to summarise the model features.

Results

The updated systematic literature search yielded 555 references published between June 2010 and August 2018. Duplicate papers ($n = 17$), conference abstracts ($n = 315$) and short-term cost-effectiveness studies carried out alongside RCTs ($n = 6$) or alongside cohort studies ($n = 13$) that did not require a model were excluded. The full texts of 68 papers featuring decision models were

reviewed, during which additional papers were excluded because the study interventions were carried out in a secondary care setting only ($n = 33$), they focused on specific subgroups of patients with CHF (e.g. diabetes or hypertension), they were a non-UK-specific adaptation of already included models ($n = 14$), or were a review of cost-effectiveness studies or methods ($n = 5$). A total of 20 manuscripts from the new search were included in the final selection. One additional study was identified through a search of references. In addition, 19 papers from the previous review by Goehler *et al.*[77] were also included. In total, 40 models were included in the review (*Figure 14*).

Included models (*Table 35*) assessed diagnostic procedures ($n = 3$),[13,234,257] disease management interventions ($n = 11$)[233,238–240,243,245,250,256,260–263] (one model was reported in two studies[262,263]) and drug interventions ($n = 26$).[224–232,235–237,241,242,244,246–249,251–255,258,259] Modelling approaches included Markov models ($n = 31$), decision trees ($n = 1$), Markov model alongside a decision tree ($n = 2$), discrete event simulation ($n = 4$) and structural mathematical equations ($n = 2$).

Modelling of disease progression

There were several recurring approaches of varying complexity of modelling CHF disease progression (see *Table 35*). Ten studies used the NYHA classes in the basis of model disease progression. Of these studies, eight used a Markov model,[224,226,235,240,248,254,258,261] one used a Markov model alongside a decision tree[244] and one used a discrete event simulation.[237]

Ten studies,[225,227,228,233,235,238,239,243,256,260] all of which used Markov models, used the number of hospitalisations for heart failure as the basis of model disease progression. A further two studies[229,230] used mathematical equations to model hospitalisations, and another[259] used types of hospitalisation (ward or intensive care unit) as model states. One study[234] used alternative definitions of CHF (symptomatic and ejection fraction) as states in their Markov model.

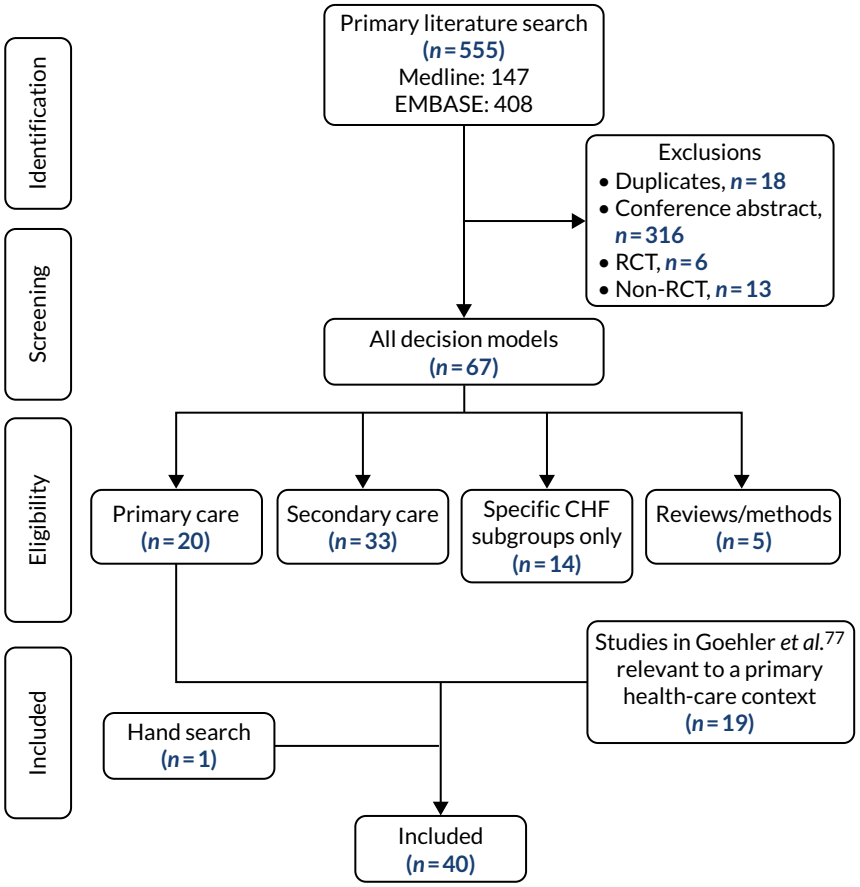


FIGURE 14 The PRISMA diagram of study selection.

TABLE 35 Overview of CHF models: study characteristics, model description, model structure and outcomes

Study (first author and year), country	Type of intervention	Target population	Perspective	Model type	Time horizon	Model structure	Outcome of the model
van Hout[224] (1993), the Netherlands	Drugs	Aged 35–85 years, II–IV NYHA class	Societal	Markov	10 years	Five states: four NYHA states, one death state	LY, costs, ICER
Paul *et al.*[225] (1994), USA	Drugs	EF < 35%, NYHA class	Societal	Markov	10 years	Six states: five hospitalisation states (0, 1, 2, 3, ≥ 4 hospitalisations), one death state	LY, costs, ICER
Glick[226] (1995), USA	Drugs	EF < 35%, NYHA class	Societal	Markov	Lifetime	Weibull model for annual survival probabilities; four NYHA classes for functional status and quality of life	LY, QALYs, costs, ICER
Delea[227] (1999), USA	Drugs	EF < 35%, mean age 60 years, II–IV NYHA class	Societal	Markov	20 years	Six states: five hospitalisation states (0, 1, 2, 3, ≥ 4 hospitalisations), one death state	LY, costs, ICER
Levy[228] (2001), Canada	Drugs	II–III NYHA class	Third party payer	Markov	20 years	Six states: five hospitalisation states (0, 1, 2, 3, ≥ 4 hospitalisations), one death state	LY, costs, ICER
Varney[229] (2001), UK	Drugs	Symptomatic HF	Third party payer	Mathematical equations	5 years	Survival model using actuarial method to estimate survival probabilities; hospitalisation rate estimated using trial data (to account for costs)	LY, costs, ICER
Gregory[230] (2001), USA	Drugs	II–III NYHA class	Not indicated	Mathematical equations	Not indicated	Survival model (sex-stratified Weibull model); hospitalisation model (exponential probability distribution model between hospitalisations) to account for costs	LY, costs, ICER
Barry[231] (2002), Ireland	Drugs	III–IV NYHA class	Not indicated	Markov	10 years	Two states: alive, dead; CHF hospitalisation state for cost only	ICER
Tilson[232] (2003), Ireland	Drugs	EF < 35%, III–IV NYHA class	Not indicated	Markov	10 years	Three states: severe HF, hospitalisation with severe HF and death	ICER
Morimoto[233] (2004), Japan	Management	EF < 40%, aged 35–85 years, II–III NYHA class	Not indicated	Markov	18 months	Six states: five hospitalisation states (0, 1, 2, 3, ≥ 4 hospitalisations), one death state	Costs, ICER
Heidenreich[234] (2004), USA	Diagnostic	Asymptomatic with EF < 40%, NYHA class	Societal	Markov	Lifetime	Four states: three HF stages [symptomatic, non-symptomatic (both with low EF) and asymptomatic normal EF], one death state. Event state of hospitalisation	LY, QALYs, costs, ICER

continued

TABLE 35 Overview of CHF models: study characteristics, model description, model structure and outcomes (*continued*)

Study (first author and year), country	Type of intervention	Target population	Perspective	Model type	Time horizon	Model structure	Outcome of the model
Cowper[235] (2004), USA	Drugs	I–IV NYHA class	Societal and third party payer	Markov	5 years	Five states: four NYHA states, one death state (probability of hospitalisations included in the model)	LY, costs, ICER
Inomata[236] (2004), Japan	Drugs	II–III NYHA class	Third party payer	Markov	5 years	Two states: alive and dead; a further 'hospitalisation due to worsening CHF' to inform costs only	LY, costs
Caro[237] (2005), USA	Drugs	Aged 41–80 years, II–IV NYHA class	Third party payer	DES	2 years	Events: hospitalisation (HF, CVD other); death (CVD, other); hospitalisation (cost and time); management (NYHA state, hospital visits, drug costs)	LY, costs, ICER
Göhler[238] (2008), Germany	Management	III–IV NYHA class	Societal	Markov	Lifetime	Five states: four hospitalisation states (index hospitalisation; rehospitalisations 1, 2 and ≥ 3), one death state	LY, QALYs, costs, ICER
Chan[239] (2008), USA	Management	EF $< 35\%$, II–III NYHA class	Health-care provider	Markov	15 years	Six states: five hospitalisation states (0, 1, 2, 3 and ≥ 4 hospitalisations), one death state	LY, cost, ICER
Miller[240] (2009), USA	Management	Echocardiographic evidence of CHF, NYHA I–III	Health-care system	Markov	Lifetime	Four states: NYHA I, II, III/IV and death	LY, QALYs, costs, ICER
Rosen[241] (2010), USA	Drugs	Symptomatic HF	Third party payer	Markov	Lifetime	Six states with combinations of major events (e.g. MI, stroke) and minor events (e.g. TIA), and non-cardiovascular and all-cause mortalities from states	LY, QALYs, costs, ICER
Cowie[242] (2011), UK	Drugs	NYHA II–III	Third party payer	Markov	Lifetime	10 states: cardiovascular events [complication-free HF; HF hospitalisation, MI (first or second) and stroke (first, second or third) and CVD and other death]	LY, cost, QALY, ICER
Moertl[243] (2012), Austria/Canada	Management	NYHA III–IV	Payer	Markov	20 years	Five states: event free, one hospitalisation, two hospitalisations, three or more hospitalisations and death	LY, cost, QALY, ICER
Ford[244] (2012), Australia	Drugs	II NYHA class	Government-funded health system perspective	Markov and decision tree	5 years	Four states: NYHA classes I–IV. A decision tree (for each NYHA class) for hospitalisation and death	LY, cost, QALY, ICER

Study (first author and year), country	Type of intervention	Target population	Perspective	Model type	Time horizon	Model structure	Outcome of the model
Thokala[245] (2013), UK	Management	Within 28 days of HF hospital admission	Health-care system	Markov	30 years	Two states: alive and dead	QALY, cost, ICER
Banka[246] (2013), US	Drugs	EF < 35%, NYHA II–III	Single-payer/vertically integrated health-care system providing full coverage	Markov	Lifetime	Two states: alive and dead	LY, cost, QALY, ICER
Ademi[247] (2014), Australia	Drugs	Aged ≥ 55 years, LVEF ≤ 30%; on hypertensive treatment, NYHA class II	Australian health-care system	Markov	10 years	Two states: alive and dead and additional cardiovascular transition states (no HF hospitalisation, HF hospitalisation)	LY, cost, QALY
Griffiths[248] (2014), UK	Drugs	Heart rate > 70 b.p.m., prior to HF hospitalisation, NYHA class II–IV	NHS	Markov	Lifetime	HF hospitalisation; cardiovascular hospitalisation, death, NYHA class, hospital length of stay	LY, cost, QALY, ICER
Lee[249] (2014), UK/Spain	Drugs	II NYHA class	Not clear	DES	Lifetime	Eight event states (other cardiovascular hospitalisation; HF hospitalisation; atrial fibrillation; adverse event; treatment continuation; devices; cardiovascular mortality; non-cardiovascular mortality)	LY, cost, QALY, ICER
Reed[250] (2015), USA	Management	Any NYHA class	Any	Individual patient simulation	Lifetime	A modified version of the Seattle Heart Failure Model in which the risk of death and treatment effects of medications were revised using recent clinical trials' data	LY, cost, QALY, ICER
Kansal[251] (2016), USA	Drugs	LVEF < 35%; resting heart rate > 70 b.p.m.; sinus rhythm, NYHA class II–IV	Third party payer	Markov	10 years	10 states: interactions of HF events (0 to ≥ 3), cardiovascular events (0 to ≥ 3) where HF ≤ cardiovascular event, and death	Life expectancy, cost, QALY, ICER
Thanh[252] (2016), Canada (AB)	Drugs	Mild symptoms aged > 55 years	Health service	DES	Lifetime	Eight event states (HF hospitalisation, other CVD hospitalisation, AE, AF, implant, CVD death, other death, end of time horizon)	Life expectancy, cost, QALY, ICER
Sandhu[253] (2016), USA	Drugs	LVEF < 40%, II–IV NYHA class	Societal	Markov	Lifetime	Six states: HF hospitalisation, non-HF hospitalisation, ED HF visit, treatment intolerance, CVD death and non-CVD death	Life expectancy, cost, QALY, ICER

continued

TABLE 35 Overview of CHF models: study characteristics, model description, model structure and outcomes (*continued*)

Study (first author and year), country	Type of intervention	Target population	Perspective	Model type	Time horizon	Model structure	Outcome of the model
King[254] (2016), USA	Drugs	Reduced EF (< 35%)	Third party payer	Markov	40 years (lifetime)	Combination of four NYHA classes and clinical events [no event, HF hospitalisation (30-day re-admission, no re-admission), death]	Life expectancy, cost, QALY, ICER
Gaziano[255] (2016), USA	Drugs	LVEF < 40%, II–IV NYHA class	Third party payer	Markov	30 years	Two states: alive (with HF) and dead with hospitalisation classed as an event	Life expectancy, cost, QALY, ICER
Dang[256] (2017), USA	Management		Societal	Markov	10 years	Eight states: three hospitalisation states (1, 2 and 3), four alive (but not hospitalised) states taking into account the number of previous hospitalisations and one death state	Life expectancy, costs, ICER
Monahan[257] (2017), UK	Diagnostic	Symptoms suggestive of HF	NHS/Personal Social Services	Decision tree	Lifetime	Taken from a previous HF Health Technology Assessment (to present the different diagnostic strategies for patients presenting with HF symptoms in primary care)	Life expectancy, cost, QALY, ICER
Liang[258] (2017), Singapore	Drugs		Health-care payer	Markov	10 years	NYHA classes I–IV and deaths; interacting with no event; HF hospitalisation (no admission; re-admission); death from CVD or other cause	Life expectancy, cost, QALY, ICER
van der Pol[259] (2017), the Netherlands	Drugs		Health-care payer	Markov	30 years	Four states: HF (home care); ward hospitalisation; intensive care unit hospitalisation; dead	Life expectancy, cost, QALY, ICER
Maru[260] (2017), Australia	Management	II–IV NYHA class	Government-funded health system	Markov	15 years	Five states: event free, HF hospitalisations (1, 2 and ≥ 3) and death	Life expectancy, cost, QALY, ICER
Grustam[261] (2018), the Netherlands	Management	Aged ≥ 70 years and I–IV NYHA class	Health care	Markov	20 years	Five states: four NYHA I–IV states and one death state; annual cycle	Life expectancy, costs, QALYs, ICER
NICE HF guideline[13] (2018), UK	Diagnostic	People with suspected or diagnosed HF	UK NHS/PSS	Decision tree/ Markov model	Lifetime	A decision tree: proportion in each disease cohort and test referral Markov model: hospitalisation and death	QALY, cost, ICER
Mohiuddin[262] (2016) and Pufulete[263] (2016/2017), UK	Management	Subgroups by age and LVEF status, NYHA class	Government-funded health system perspective	Markov	30/15 years	Two states (alive and dead); probabilities of death and hospitalisation recorded as an event that has an impact on the quality of life and costs	Life expectancy, cost, QALY, ICER

b.p.m., beats per minute; DES, discrete event simulation; ED, emergency department; EF, ejection fraction; HF, heart failure; ICER, incremental cost-effectiveness ratio; LY, life-year; MI, myocardial infarction; TIA, transient ischaemic attack.

A two-state Markov model using 'alive' and 'dead' states was used in six studies.[226,231,236,245–247] Five Markov models[237,241,242,252,253] used CVD events, including decompensated heart failure, myocardial infarction, stroke/transient ischaemic attack and cardiovascular death in modelling CHF progression. Three studies used composite states consisting of the NYHA class and number of hospital admissions for heart failure to model progression.[249,254,258] Two further Markov models[248,251] used hospitalisation for heart failure combined with CVD events to model disease progression.

More recent studies were more likely to have a more detailed model structure, with all four studies having at least 10 states published post 2011.[242,251,254,258]

Patient characteristics

Eleven studies considered a range of patient characteristics at entry into the models. In six studies non-fatal heart failure hospitalisations at entry influence the probability of death.[245–247,255,262,263] One study[245] considered the impact of the time since discharge from heart failure hospital admission on the probability of death. One study[238] used an age and sex adjustment for non-CVD death and overall mortality. In one study,[248] which used parametric risk equations to model composite NYHA and CVD end points in the model, a range of baseline sociodemographic characteristics, use of heart failure medications or other cardiac therapies, prior cardiovascular history and biological characteristics were used. A further study[250] used the Seattle Heart Failure Score (and updated it in the model) to inform the cause and probability of death.

More recent studies were more likely to incorporate patient characteristics in their models. All studies that considered interaction states were published after 2012.[248,249,251,254,258] Similarly, all seven studies[245–247,255,256,262,263] one used a Markov model alongside a decision tree[244] that considered the impact that heart failure hospitalisation had on death rates were published post 2013. Models published earlier than 2013, were more likely to use constant transition probabilities over time.

Data sources used to populate the models

End points

Thirty-nine economic models[13,224–227,229–263] used data from RCTs to model CHF and disease progression, with the remaining study[228] using cohort and meta-analysis data (*Table 36*). Twenty-six studies used only RCT data. The remaining studies used RCT data together with data from cohort studies ($n = 4$),[230–232,250] administrative data ($n = 8$)[13,235,236,240,256,259,262,263] or some combination of these ($n = 2$).[224,244] A total of 22 different RCTs were used across the 43 studies. One RCT explicitly stated that it had recruited from primary care.[257]

There were seven UK-based models; of these, six used RCT data only or RCT data alongside external data.[13,242,245,248,249,262,263] There was one study[262] that used data from CPRD linked with mortality data from the Office for National Statistics along with hospital rates based on published cohort data. One study[242] used expert opinion to model disease rates after the end of the trial.

Treatment effects on disease end points were integrated through adjusting the probabilities of death and hospitalisation ($n = 24$), and through direct estimation of separate transition probabilities for each intervention group from the trial data ($n = 16$).

Cost

Most studies used administrative unit cost data such as UK-based reference costs and and US prices data ($n = 29$) (see *Table 36*). Two studies used micro-costing methods.[231,232] Twelve studies used some RCT data, of which seven used RCT data in conjunction with other sources such as unit costs from the German diagnosis-related group grouper, the UK Healthcare Resource Groups costs or US Medicare costs of tests and drugs.[238,245,246] There was one study that used cohort data to estimate costs.[262] Expert opinion to estimate resource use was used in two studies.[242,245]

TABLE 36 Overview of CHF models: data sources for disease progression, costs and quality of life

Study (first author and year), country	Data to inform disease end points in model	Individual patient characteristics in model	Data to inform costs in model	Data to inform quality of life in model
van Hout[224] (1993), the Netherlands	Unclear	Unclear	Unclear	Not collected
Paul[225] (1994), USA	Transition probabilities estimated using available trial data	Transition probabilities depend on time	US administrative data used to estimate a cost for a hospitalisation. Drug costs taken from retail pharmacy survey	Not collected
Glick[226] (1995), USA	Trial data used to estimate Weibull model for survival and the transition probabilities between NYHA states. Post-trial probabilities adjusted to reflect an increased all-cause mortality. Administrative data used to estimate ambulatory care event rates	Unclear	US administrative data used to cost all events (including death) and therapy	The visual analog scale, the Ladder of Life questionnaire, data in the trial was used to estimate quality of life for each NYHA state
Delea[227] (1999), USA	Trial data (from two studies): published data used to 'solve' for the different state-specific probabilities of hospitalisation and costs	Unclear	Drug and event costs taken from various US generic sources used to estimate cost of events and baseline costs	Not collected
Levy[228] (2001), Canada	Cohort data for monthly transition probabilities of event. Random effect meta-analysis of placebo-controlled trials used for treatment effect	Age-specific (5-year age bands) transition probabilities and length of hospital stay	Author assumptions for quantity; daily costs from administrative sources used to estimate costs of hospitalisation and death	Not collected
Varney[229] (2001), UK	Survival was estimated using the actuarial method using aggregated trial data; rate of hospitalisation estimated using aggregated trial data	Unclear	Administrative data and trial data used to estimate cost of hospitalisation and multiplied by hospitalisation rate	Not collected
Gregory[230] (2001), USA	Trial data and Framingham Heart Equations used to estimate lifetime survival distributions. Published data for estimating hospitalisations	Gender-stratified Weibull models	Administrative data used to derive a cost model estimating the relationship between the admissions and hospitalisation/outpatient/professional costs	Not collected
Barry[231] (2002), Ireland	Cohort data (hospital study) for probabilities of death and hospitalisation. Treatment effect from trial data	None (fixed rates)	Previous micro-costing for cost of drugs and hospitalisation	Not collected

Study (first author and year), country	Data to inform disease end points in model	Individual patient characteristics in model	Data to inform costs in model	Data to inform quality of life in model
Tilson[232] (2003), Ireland	Cohort data from hospital clinic (Ireland) (12-month period) for probabilities of death and hospitalisation. Treatment effect from trial data	None	Previous micro-costing used for cost of hospitalisation (carried out in the same hospital)	Not collected
Morimoto[233] (2004), Japan	Delea *et al.*[227] used for comparator probability of admission (trial data). Troughton *et al.*[264] used to estimate effects of treatment	None	Delea *et al.*[227]	Taken from external time trade-off study – one quality of life for all alive states
Heidenreich[234] (2004), USA	Framingham Heart Study used for specificity and sensitivity of test. Trial data used to estimate event rates	Sex-specific specificity and sensitivity of BNP test	Administrative data used for resource use and costs for states	Time trade-off data from a previous trial used to estimate weights for asymptomatic/symptomatic states
Cowper[235] (2004), USA	Trial data used for transition probabilities between NYHA states. Observational data used to estimate number of allowed hospitalisations. Trial data supplemented by observational studies used for estimating treatment effects		Administrative data for each NYHA state and inpatient/outpatient states	Not collected
Inomata[236] (2004), Japan	Trial data and administrative data (non-CHF-related mortality)		Cohort data used to cost an outpatient schedule	Not collected
Caro[237] (2005), USA	Event rates taken from trial results and assigned to relevant states	Age, sex, NYHA class and EF assigned to each patient	Administrative data and resource-use profiles generated by the authors	Not collected
Göhler[238] (2008), Germany	Weibull and logistic regression of trial data for transition probabilities. Meta-analysis for effectiveness	Mortality risk a function of age and sex	Trial data for cost of hospitalisation; survey of doctors for resource use; treatment costs from administrative data (German diagnosis-related group grouper)	Trial data by using multivariate regression for estimating utilities allocated to each state
Chan[239] (2008), USA	Trial data (from two studies): published data used to 'solve' for the different state-specific probabilities of hospitalisation and costs		Estimated based on a review of literature on associated costs	Not collected
Miller[240] (2009), USA	Trial data used to infer transition rates. Administrative data used to adjust mortality rates for age	Age	Trial data used for resource use. Costs of resources from administrative data	Baseline study SF-36 results used to develop utility adjustment weights

continued

TABLE 36 Overview of CHF models: data sources for disease progression, costs and quality of life (*continued*)

Study (first author and year), country	Data to inform disease end points in model	Individual patient characteristics in model	Data to inform costs in model	Data to inform quality of life in model
Rosen[241] (2010), USA	Trial data used for a Kaplan–Meier time to first event analysis (5-year probabilities assumed to be constant to year 10), after which pooled hazard ratios across treatments were used. Second event rates pooled estimates from trial data		Drug and event costs from published external sources	The EuroQol-5 Dimensions index scores from Sullivan *et al.*[265]
Cowie[242] (2011), UK	Trial data (both arms) used to estimate transition probabilities for the trial duration. Extrapolation period used literature and expert opinion assuming no difference between trial arms		Expert opinion and external data sources used to estimate the cost of each station/transition	Trial data used to estimate baseline utility. Expert opinion and external study data used for the impact that events had on quality of life
Moertl[243] (2012), Austria/Canada	Trial data used (and extrapolated) to estimate transition probabilities	Data stratified by beta-blocker use	Trial costs (hospitalisation) and administrative data (medication costs)	Derived from trial data (patient questionnaire)
Ford[244] (2012), Australia	Trial data informs NYHA transitions. Administrative and cohort data inform other transitions	NYHA I to IV classes through model states	Administrative costs used for event, hospitalisation. Trial data used for drug costs	Trial data (same as for end points) used to estimate quality of life. Fixed disutility for hospitalisations
Thokala[245] (2013), UK	Trial data used to estimate monthly probabilities of death	Non-fatal hospitalisation influences the probability of death. Length of time since hospital discharge influence the probability of death	UK Healthcare Resource Group cost of HF and other hospital admissions; The Trans-European Network-Home-Care Managements System (TEN-HMS)[162] trial; clinical opinion (programme costs)	Literature search used to estimate mean quality of life: first and subsequent years post HF admission; quality of life disutility with hospital admission
Banka[246] (2013), USA	Mortality rates and probability of hospitalisation derived from trials of each treatment comparison	Non-fatal hospitalisations influence the probability of death	Trial data used for costs of care; costs of test and drugs was taken from US Medicare data	The same health utility was applied for all non-fatal health states
Ademi[247] (2014), Australia	The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)[266] trial data for placebo arm's event rates and hazard ratios between trial arms	Non-fatal hospitalisations influence the probability of death	Data from Australia-specific sources used to estimate cost of events	Single quality of life applied to the alive state; used in Ford *et al.*[244] (Australian Study) derived from CARE-HF trial quality of life presented in Yao *et al.*[267]

Study (first author and year), country	Data to inform disease end points in model	Individual patient characteristics in model	Data to inform costs in model	Data to inform quality of life in model
Griffiths[248] (2014), UK	Trial data used to generate parametric equations for cardiovascular mortality, hospitalisation and NYHA class	Baseline sociodemographic characteristics; baseline use of HF medications; baseline use of other cardiac therapies; prior cardiovascular history; biological characteristics; NYHA classes through model states	UK-based administrative costs for hospitalisations; drugs and deaths	Multilevel model using the EuroQol-5 Dimensions results gained in the Systolic HF Treatment with the If Inhibitor Ivabradine Trial (SHIFT):[268] prediction based on treatment allocation, baseline characteristics, NYHA class (time updated) and hospitalisation episode
Lee[249] (2014), UK/Spain	Trial data used to generate parametric risk equations for events	Patient characteristics used in parametric risk equations	Trial data used for treatment costs. Proportions experiencing events used to estimate cost difference between arms and types of events	Formula from Göhler *et al.*[238] used with baseline trial data
Reed[250] (2015), USA	Trial data (four studies) and observational cohorts used to derive competing risk regression for cause of death; various other studies used for treatment effects	Seattle Heart Failure Score (time updated) has an impact on cause and probability of death	Trial data used to estimate impact of Seattle Heart Failure Model score on medical resource use	Trial data used to estimate impact of Seattle Heart Failure Model score on health utility
Kansal[251] (2016), USA	US claims data and trial data used to estimate event rates and adverse events data; post hoc analysis of trial data used for cardiovascular mortality rates	Interaction between cardiovascular events and HF events through model structure	Administration and physician fee and coding data	Regressions using trial data used to estimate the change in baseline EuroQol-5 Dimensions index score due to event
Thanh[252] (2016), Canada	Trial data used (via parametric risk equation) to estimate end points	Age randomly assigned to patients	Pharmaceutical report and administrative data	Formula from Göhler *et al.*[238] applied using trial data
Sandhu[253] (2016), USA	Placebo arm of trial used (via parametric survival equations) to estimate end points		Administrative data (adjusted by age and NYHA class)	Trial data (two studies) for baseline utility, treatment and disutilities
King[254] (2016), USA	Life tables and trial data (two trials) used to estimate event rates	Structural: interaction between cardiovascular events and NYHA classes	Study of electronic records used for hospitalisation; administrative data for drug costs	Trial data used to estimate quality of life for the NYHA classes. Fixed disutility for hospitalisations
Gaziano[255] (2016), USA	Data from a RCT used to estimate all transition probabilities and hazard ratios	Non-fatal hospitalisations influence the probability of death	Administrative data and wholesale costs used	Trial data used to calculate a mixed-effects model based on EuroQol-5 Dimensions at baseline, age, time, hospitalisation and treatment status

continued

TABLE 36 Overview of CHF models: data sources for disease progression, costs and quality of life (*continued*)

Study (first author and year), country	Data to inform disease end points in model	Individual patient characteristics in model	Data to inform costs in model	Data to inform quality of life in model
Dang[256] (2017), USA	Trial cohorts and administrative data used to model the transition rates	Non-fatal hospitalisations influence the probability of death	Costs taken from a literature review	Not collected
Monahan[257] (2017), UK	Individual participant data from a prospective observational study was used to estimate probability of decision tree branches – probability of patients taking each branch of the decision tree. Framingham equations used to estimate prognosis post HF diagnosis		UK-based administrative data used for unit costs	Trial data (from the group who completed the 6-month questionnaire) used to estimate QALYs gained
Liang[258] (2017), Singapore	Transition probabilities for end points estimated using parametric risk equations using data from a RCT subpopulation (Asian)	Structural: interaction between HF events and NYHA classes	Administrative data used to estimate hospital costs	Trial data used to estimate quality of life for the NYHA classes. Fixed disutility for hospitalisations
van der Pol[259] (2017), the Netherlands	Trial data, other study data and administrative data used to estimate the transition probabilities and treatment effects		Trial data and general Dutch administrative data used to estimate costs	Trial EuroQol-5 Dimensions data (UK based) used to estimate quality of life using the NYHA distribution in a trial
Maru[260] (2017), Australia	Weibull model used to calculate the time-dependent probability of death adjusting for baseline covariates. Hospital re-admissions estimated using study data and assumptions beyond trial duration		Study data used to estimate cost of hospitalisation and community-based care with assumptions for increase in costs beyond the trial	Trial data (using regression) used to estimate baseline utility and the disutility due to hospital re-admission
Grustam[261] (2018), the Netherlands	Trial data used to estimate the transition probabilities		Dutch administrative data used for all costs	Trial data informed the estimate of the utility using Dutch weights
NICE HF guideline[13] (2018), UK	RCT data used to estimate transition probabilities and diagnostic pathways. UK life tables were used for all-cause mortality. Meta-analysis was used for the treatment effects		Administrative costs and author assumptions for resource use	Trial data used to estimate utility for patients with CHF diagnosis
Mouhiuddin[262] (2016) and Pufulete[263] (2016/2017), UK	Administrative (CPRD–ONS) data used for mortality and hospitalisation; trial data used to estimate treatment effects	Non-fatal hospitalisations (and age) influence the probability of death	General UK-based sources used to estimate medication and hospitalisation costs	Trial data used to estimate quality of life utilities in model states

EF, ejection fraction; HF, heart failure; ONS, Office for National Statistics; SF-36, Short Form questionnaire-36 items.

Of the eight UK-based studies, most used administrative data including the *British National Formulary*, NHS Reference costs, Healthcare Resource Groups costs, Personal Social Services Research Unit costs, Prescription Cost Analysis and Scottish National Tariffs ($n = 5$). One study used RCT data alongside administrative data and expert opinion,[245] one used expert opinion on resource use alongside administrative data[242] and one model used trial data.[249]

Quality-of-life data

In total, 30 out of the 40 included models evaluated patients' quality of life in the model (see *Tables 35* and *36*).

The majority of studies used data about patients' quality of life from RCTs ($n = 23$), of which a total of 15 different RCTs were used. Of these, one study used the trial data in conjunction with expert opinion about the quality of life of patients with CHF after a myocardial infarction or stroke.[242] There were five studies that used previously published data regarding quality of life to populate their models.[233,234,241,245,246]

Seven out of the eight UK-based models incorporated quality-of-life data. Six of these used quality-of-life data from RCTs[242,248,249,257,262,263] and one used previously published data.[245]

The majority of the studies that included information on quality of life evaluated the impact that treatments had on quality of life through the transition probabilities in the model [i.e. quality-of-life estimates were applied to the states in the Markov model and treatment affected progression between the states ($n = 17$)]. There were two studies that directly derived utility estimates for patients using equations based on a range of patient characteristics.[248,255] Five studies included a direct effect of treatment on quality-of-life utility. Four studies evaluated effect of treatment on quality of life solely through its effect on the disease progression between model states.[246,247,254,261]

Discussion

This review identified 40 economic models used to evaluate interventions for CHF patients with potential relevance to the primary care setting. A number of different model structures were employed with model complexity, judged by the number of model states or links between states, increasing over time. Individual patient characteristics were not commonly considered with only 11 (28%) of the models including these, although their use has increased in more recent studies. There was only one study that explicitly used patient data from primary care. The majority of studies used data from CHF patients recruited from hospital settings.

All studies used data from RCTs to inform their model parameters, with source trials frequently completed some years previously and unlikely to be representative of the current CHF population and disease management. For example, one study published in 2008[239] used data from a trial that ran from 1986 to 1999.[269] In addition, trials recruited mostly in secondary care and their participants were often much younger than typical CHF patients seen in primary care. Other common sources of data were administrative data sources, mainly for all-cause mortality rates ($n = 7$). Data from the Framingham Heart Study was used to estimate CVD event risks in three studies.[230,234,257] Further cohorts were used, including the COPERNICUS cohort and a hospital clinic-based cohort.[232,270]

Over time, the CHF patients' NYHA classes were frequently used to inform the structure of disease models. However, the limited duration of most studies, the slow progression between NYHA classes in the stable CHF patients typically studied and the limited measurements of NYHA class during the duration of studies make this disease measure of limited longitudinal value. Modelling the number of hospital admissions, an alternative approach to measuring disease progression, was another common approach. However, hospital admissions are affected by health services provision and quality of care

and, therefore, not necessarily appropriate. The difficulties of identifying appropriate proxies for disease progression persist in developing CHF models.[77]

A number of studies used patient characteristics in risk equations to take into consideration individual patient's disease risks. Incorporating the information from previous heart failure hospitalisations (through either the number of hospitalisations or the time since hospitalisation) was the most common way of incorporating patients' disease severity; however, being an indirect proxy measure, it has limited ability to inform treatment and disease management decisions for individual patients. Further work on markers of CHF severity and factors associated with them is required to improve patient risk stratification in CHF.

This review has found that data from well-characterised CHF patient cohorts in primary care are lacking. Data from clinical trials have filled the gap but their use jeopardises the generalisability of findings to the population seen in primary care. The ECHOES cohort,[53] which includes > 6000 patients with CHF followed up for at least 15 years, is one such cohort that could be used to derive information on transitional probabilities and quality-of-life data for use in economic models.[50] Routine health-care data, such as data in primary care databases and Hospital Episode Statistics, could inform factors such as CHF hospitalisations and death rates but are limited with respect to data about NYHA class or other markers of disease severity and progression.

Data about patients' quality of life and costs specific to the CHF population are also lacking. Studies often used quality-of-life estimates derived from trials, and, as mentioned earlier, the duration of these trials may not be sufficient for the long-term impacts that disease progression has on quality of life to have emerged. Data about health-care costs are routinely collected in administrative data sources but are unlikely to inform models at the required granularity of disease severity (e.g. by NYHA class or patient comorbidities). More detailed quality-of-life data, resource use and cost information could be collected as part of future CHF patient cohorts.

Two broad areas in need of further research are identified as highly informative for future assessment of monitoring strategies of CHF in primary care. First, the increased use of well-characterised CHF patient cohorts in primary care, including data regarding disease status, disease progression, quality of life and health-care use, should be encouraged. Second, a broad consensus on appropriate markers of CHF disease severity and progression over time in primary care could be helpful in guiding prospective data collection as well as informing models of disease that are a better fit to assess the increasing range of CHF interventions.

Limitations

In this review, we did not assess whether or not the approaches employed in modelling CHF and effects of interventions were appropriate but instead we summarised model features and discussed these with respect to their suitability in assessing the monitoring and management of CHF in primary care.

Conclusion

A number of decision-analytic models in CHF are currently available and could be considered in assessments of the monitoring and management of interventions for patients with CHF in primary care. The majority of these models, however, were informed using data from CHF patients seen in secondary care who were recruited to randomised clinical trials up to 20 years previously. The use of more detailed data on CHF patients typically seen in contemporary primary care, including patient characteristics and markers of progression of CHF, should be encouraged.

Appendix 23 Stakeholder group: terms of reference and membership

Date: 21 May 2014, version: 0.3.

The role of the group

The role of the stakeholder group is to represent the views of health practitioners and patients (PPI) in the research activities conducted as part of the Monitoring Long Term Conditions programme. The group has been established for the purpose of this programme and will be active for its duration (until 31 May 2019).

Tasks

- Provide views on the plans for design, implementation and evaluation of applied interventions.
- Participate in developing the plans for understanding patient and GP factors associated with monitoring in CKD and CHD.
- Contribute to plans to explore the views of patients and practitioners of potential changes to type of test used, frequency of testing and setting of testing (i.e. self-monitoring).
- Guide and advise on the dissemination of individual research projects in the programme.
- Attend senior management meeting (optional).
- Representation on advisory group.

Membership

- One panel that includes practitioners and patients; 12 people (six patients or lay persons, three nurses – patient-facing, one pharmacist, two clinicians – at least one GP).
- For the PPI element, aim to have representation for non-CKD, non-CHF, CKD, CHF and, if possible, at least one member with both conditions.
- Aim to have group set up for October 2014.
- Members would be expected to attend at least one of the biannual meetings and to provide periodic feedback on research outputs (in person or in writing).

Review

The membership and commitment to the group will be reviewed half-way through the programme (autumn 2016).

Working methods

- Face-to-face meetings every 6 months.
- A maximum of 2 hours will be allocated for the stakeholders' meeting.
- An agenda and relevant paperwork will be circulated via e-mail 1 week before the meeting. This agenda will be initially created by the research team, but can be modified according to the group's views.

- Chairing and minute-taking will be done by members of the research team.
- During the meeting, an update to the projects in the programme will be presented.
- Views and opinions will be collected during the meeting. For members unable to attend, views and opinions can be given via e-mail.
- Minutes from these meetings will be circulated within 1 month after the meeting.
- After the face-to-face meeting, members of the group will be welcomed (but not obliged) to attend the senior management meeting (approximately 2 hours).
- In the first instance, all material will be circulated via e-mail. If necessary, alternative methods for sharing information will be considered.

Payment and support (patient and public involvement only)

- Patient and public involvement members will be remunerated for their time at a rate of £150 per day.
- Travel expenses will be paid, in advance when possible, so that members will not be out of pocket.
- Training and support for PPI members will be provided, if required, by the NDPCHS.

Definition of terms

- Chronic kidney disease: for the purposes of this programme, it is early stages, that is when no or minor symptoms exist.
- Chronic heart failure: for the purposes of this programme, this is symptomatic, and therefore needs to be actively managed by a clinician.

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