An evidence-based evaluation of the clinical and cost effectiveness of foot ulcer risk assessment and structured care interventions for people with diabetes.

Protocol

BACKGROUND

Diabetes-related foot ulcers give rise to considerable morbidity and generate a high monetary cost for health and social care services. (1) They precede 80% of diabetes-related lower extremity amputations (LEAs). (2) Routinely collected data from Scotland indicate that the incidence of diabetes-related foot ulcer in 2014 was 4.9% of the diabetic population. (3) An estimated prevalence of 2.5% across the whole of the UK diabetic population generates an annual economic burden of £300 million to provide community and primary health care for those with the condition. (4) The additional cost of LEAs more than doubles the cost to around £662 million. (4) High levels of variation in rates of diabetes-related LEAs between primary care trusts (PCTs) in England have been reported and one possible explanation for these differences in patient outcomes might be differences in the delivery of care. (5) For those who experience a diabetes related foot ulcer, the 5-year survival is poor with mortality estimates of between 25% and 50% consistently reported over a 20 year period in the UK and other parts of Europe. (6)

There are many clinical prediction rules (CPR) in existence to assess risk of foot ulceration in diabetes, but few have been subject to validation. (7) In the UK, two diabetes clinical guidelines (8,9) give advice about the management of the foot, and risk assessment procedures and preventative interventions for those found to be at risk are recommended. But the advice these influential documents contain is predominantly based on clinical consensus and both guidelines omit highly relevant data. (10,11,12,13,14,15) Further robust evidence to show that the routine surveillance that is advised reduces the number of diabetes-related foot ulcers or LEAs is scarce. (16)

WHY THIS RESEARCH IS NEEDED NOW

The current NICE clinical guideline for the management of the diabetic foot recommends people with diabetes have a foot examination involving 8 elements and a vascular assessment with an ankle brachial index test, every year. For those judged to be at moderate or high risk, monitoring is escalated to 6 monthly intervals and up to a maximum frequency of every week. (8) As peripheral neuropathy, the most common foot complication of diabetes, is irreversible these intensive monitoring intervals are unlikely to positively influence patient outcomes. The recommendations from the diabetes guideline from SIGN (synonymous with the Scottish Clinical Information - Diabetes (SCI Diabetes) computerised decision support tool)) includes a foot examination involving 5 risk factors and advocates the use of some expensive specialist equipment not readily available outside of specialist care settings. (9) The SIGN diabetes guideline states that the frequency of monitoring should be at least annually, but concedes the optimal frequency is unknown, citing evidence from one cohort study that low risk patients had a 99.6% (95% CI 99.5% to 99.7%) chance of being ulcer-free at 1.7 years. (17) The chief investigator and a statistician co applicant (FMC) of this application led a systematic review and meta-analysis of Individual Patient Data (IPD) using data collected from patients worldwide (Prediction Of Diabetic foot UlcerationS – PODUS) (18). This enabled the external validation of a predictive model involving only 3 predictor variables; insensitivity to a 10-g monofilament; absent pedal pulses; and a history of ulceration or LEA, all easy and cheap to obtain and therefore likely to be used in clinical practice. These 3 predictors also performed well in an external validation using an independent dataset. However, the results of the PODUS analyses were expressed as summary odds ratios from a meta-analysis, which do not readily allow clinicians to assess the risk of ulceration for individual patients. We propose to develop a clinical prediction rule based on the PODUS analyses. We aim to develop a simple scoring system to identify patients at higher risk of ulceration.

We are aware the majority of the 1221 foot ulcers experienced by 16385 patients occurred two years after risk assessment supporting a recommendation for a two-year monitoring frequency for those at low risk. Small risk reductions in very bad events can be worthwhile. What is not clear however is how often people who are at moderate or high risk should be tested.

It is reasonable to expect that once a person is identified as being at moderate or high risk of developing a foot ulcer, effective preventative measures will be available. Unfortunately, this might not be the case. Both UK national diabetes guidelines advise that patients in the higher risk categories are referred to a multidisciplinary foot clinic for specialist care, but there is a lack of evidence to show whether these expensive teams of clinicians and resource-intense arrangements result in fewer lesions. Furthermore, the nature and effect of the particular interventions they provide and the best composition of the specialist team are unclear. (19,20,21) Routine risk assessments for bad outcomes without effective preventative interventions might only result in worried patients. However, an effective clinical risk score could allow diabetic patients at high risk to be triaged into more effective but more expensive preventative regimens (possibly including more frequent monitoring). The benefit of greater frequency of monitoring could result in that ulcers being detected at an earlier stage and that this would lead to better outcomes. However, high performance monitoring is more costly. Therefore we need to evaluate the cost-effectiveness of different monitoring frequencies.

It has been suggested that a large, robust randomised controlled trial to evaluate the effect of a CPR used at optimal monitoring frequencies to underpin a stratified approach is overdue, with a thorough, concurrent evaluation of the cost effectiveness of this type of care pathway. (22,23) However, each of the necessary elements of the pathway remains in need of evaluation to ensure the creation of a truly evidence-based clinical pathway. We therefore propose to conduct research to create an evidence-based clinical pathway to identify patients at risk of foot ulceration and provide them with interventions likely to produce improved outcomes.

We plan to compare the cost-effectiveness of the evidence-based clinical pathway with those recommended in the current diabetes clinical guidelines in the UK. (8,9) Given the increased prevalence of diabetes such an evidence-based approach could replace the frequent, detailed foot examinations people with diabetes currently receive, identify effective preventative interventions and reduce the high burden of costs on NHS services tasked with delivering foot care for people with diabetes.

AIMS AND OBJECTIVES

Aim

We aim to undertake an evidence-based evaluation of the clinical and cost effectiveness of the foot ulcer risk assessments and structured care interventions for people with diabetes.

Research questions

Research question 1.

(i) What is the estimated clinical and cost-effectiveness of the use of a validated CPR as part of structured care to reduce the incidence of diabetic foot ulcers?

Research question 2.

(ii) What is the likely clinical and cost effectiveness of alternative strategies including monitoring intervals?

Research question 3

(iii) Is there potential worth in undertaking further research, particularly a randomised controlled trial?

Objectives
Our research objectives are to produce an evidence-based clinical pathway by;

1. Extending (developing) our existing prognostic model into a CPR and externally validating it:
2. Conducting a survival analysis of the time to ulceration to inform the economic model:
3. Performing an overview of systematic reviews to identify the effects and costs for available interventions (simple interventions such as pressure relieving insoles and complex interventions such as specialist foot care teams): Then;
4. Combining the evidence from i, ii and iii in a cost effectiveness decision model framework and analysing alternative clinical and cost effective regimens at different monitoring intervals:
5. Conducting a value of information analysis.

RESEARCH PLAN

DESIGN AND THEORETICAL/CONCEPTUAL FRAMEWORK

RESEARCH QUESTION 1
What is the estimated clinical and cost-effectiveness of the use of a validated CPR as part of structured care to reduce the incidence of diabetic foot ulcers? The development of the evidence based clinical pathway.

OBJECTIVE 1: DEVELOPMENT OF THE CPR

THE CLINICAL PREDICTION RULE
We aim to develop a simple scoring system to identify patients at higher risk of ulceration. We will develop a logistic regression model and used the method of Steyerberg (24) to create a scoring system for the coefficients of the logistic regression model. The stages are;

i. Multiply and round coefficients
ii. Estimate a multiplication factor for the scores
iii. Estimate the intercept

DESCRIPTION OF THE DATA
We intend to use the PODUS individual patient data assembled during our previous work which comprises 10 datasets from separate cohort studies. Of these, 8 cohort datasets are held securely by the University of Edinburgh, 1 is available via a Safe Haven facility, and the last is held by the University of Washington. These have already been cleaned, checked, and used for analyses by the PODUS group. Full details of the systematic review and meta-analysis used to identify, appraise, and summarise the data are given in our earlier work (18), and will only be briefly repeated here.

TARGET POPULATION
Adults with a diagnosis of diabetes mellitus (type 1 or 2)

INCLUSION EXCLUSION CRITERIA
The inclusion and exclusion criteria for the PODUS study were; age>18 years, a diagnosis of diabetes (type 1 or type 2). .
We have presented clear inclusion and exclusion criteria for the systematic overview of evidence of interventions the method of which is presented separately to improve the clarity of the project plan.

SETTING CONTEXT
The PODUS study cohorts collectively include patients from a wide spectrum of people with diabetes, from low-risk community-based settings to high risk patients who are managed in secondary care. We are therefore able to produce evidence that is generalizable across health care settings to the general diabetic population.

SAMPLING
Our sample of patients' data was compiled during the PODUS project (118). In total the PODUS dataset includes explanatory variables from 16385 patients with 1221 ulcers at follow-up. All datasets include basic demographic data, diabetes specific data (e.g. previous history of ulceration), and foot specific data (e.g. presence/absence of pedal pulses).

DATA COLLECTION

We propose to undertake a survival analysis of data sets with time-to-foot ulcer as the outcome variable to provide data to inform the basis of our analysis of the best monitoring interval for risk assessments (described in detail below). In order to make this analysis as robust as possible we plan to conduct a long term follow-up of patients from one of the PODUS cohort studies. We will obtain these follow-up data from hand-held podiatry records of patients for which consent was obtained.

DATA ANALYSIS

We propose to undertake a one-step meta-analysis of only the 8 datasets held at the University of Edinburgh as a one-step meta-analysis requires the datasets to be combined. We will focus on the predictors that survived validation in the University of Washington dataset: monofilaments, pedal pulses, and previous history of foot ulceration. Again, to maximise the use of the data, we will use logistic regression and express the results as odds ratios. Moreover, since we will be using a one-step meta-analysis rather than a two-step, we will be able to explore the effect of study and use the logistic regression equation to calculate risk for individual patients.

However, regression equations are not widely used by clinicians to predict risk for individual patients, but some CPRs, based on regression equations, are, for example the Wells score for DVT. Appealing characteristics of CPRs include simplicity of calculation and ease of memorisation. To turn the logistic regression equation into a CPR, in essence, we will use the regression equation to calculate the probability of ulcer and assigning scores to those probabilities based on the coefficients of the regression equation. We shall check the performance of the CPR using discrimination and calibration statistics and graphs (AUC, ROC plot, Brier score, calibration slope, calibration-in-the-large, and calibration plots). We will also use Leave-One-Out cross-validation to assess model prediction. We will also validate the CPR in the Safe Haven dataset and the University of Washington dataset, and produce the same discrimination and calibration statistics and graphs. Including study as an effect in the one-step meta-analysis means we can assess the performance of the CPR in high risk versus low risk settings. We will also discuss the format of the CPR with clinical colleagues to ensure its ease-of-use. We are aware that CPRs have to be simple to use otherwise they are burdensome to health professionals

OBJECTIVE II: THE OPTIMAL MONITORING INTERVAL

We will also investigate how frequently patients should be monitored. Three of the PODUS datasets include time-to-ulceration, monofilament and pulses data. We can use these data to provide estimates for the health economic model regarding optimal frequency of modelling.

We suspect that the very small proportion of ulcers found in the Crawford dataset was due to the short length of follow-up, which was only 1 year, whereas in the other datasets most ulcers develop more than 1 year post baseline tests. We are therefore planning to follow up this cohort of patients via their hand held podiatry records to increase the length of follow-up in the Crawford (10) dataset and estimate that another 100 patients with ulcer will be identified.

Although the time-to-ulcer data comprises less than half the total PODUS dataset, it comes from 4881 patients – a large dataset. We can use this data to provide hazard ratios, estimates of the rates of ulceration, and estimates of sensitivity and specificity of the CPR and other risk assessment tools (e.g. NICE and SIGN guidelines) calculated for different time periods as required by the health economic model.

The identification of the optimal screening interval base-case will require an estimate of the potential effectiveness and cost-effectiveness of the clinical risk score calculated during patients' annual reviews based on the PODUS time-to-event data. This corresponds to the intent to develop a simple to use screen that can be used during routine assessments for people with diabetes. We will then estimate the rate at which the risk score varies and will try to estimate its effectiveness when applied more frequently at six monthly intervals and less frequently at bi-annual intervals using a hidden Markov chain analysis.

We will use SAS 9.4 (www.sas.com) and R 3.2.2 (https://cran.r-project.org/) for all analyses.

OBJECTIVE III: AN OVERVIEW OF THE EVIDENCE OF THE EFFECTIVENESS OF SIMPLE AND COMPLEX INTERVENTIONS (STRUCTURED CARE) TO PREVENT FOOT ULCERATION IN PEOPLE WITH DIABETES MELLITUS (DM).

We will undertake an overview of systematic reviews to derive estimates of the effects of individual preventative interventions and specialist multidisciplinary teams for foot ulcers in people with diabetes.

We are aware of important systematic reviews evaluating the effects of complex and simple interventions in the prevention of foot ulcers in people with DM that are published in the Cochrane Library. (19,20) There are also non-Cochrane systematic reviews in existence and our overview of reviews will include both Cochrane and Non-Cochrane reviews, in accordance with eligibility criteria presented below.

Our purpose is to identify effective interventions for inclusion in our evidence-based clinical pathway and ultimately the economic model, where these interventions make sense to health professionals involved in the care of people with diabetes. The decision to include interventions in the economic model will be informed by (i) the volume of data; (ii) the direction of effect and (iii) statistical robustness of the estimates and (iv) the opinion of NHS colleagues on our steering committee about the generalisability (external validity) of the interventions to their clinical practice.

Research methods
We will ensure the best methodological standards are adopted in the conduct of this overview of systematic reviews by adhering to the processes described in the Cochrane Handbook and from an overview of systematic reviews which focuses on diabetes-related foot interventions (dressing for diabetes-related foot ulcers) which was published in the Cochrane library in 2015. (26,27).

Objectives
Primary objective
To summarise the evidence from systematic reviews of randomised controlled trials of the effectiveness of simple and complex preventative interventions for foot ulceration in people with diabetes mellitus (DM).

METHODS
We will ensure the population (study inclusion and exclusion criteria) and the research questions for all systematic reviews are common to all reviews considered for inclusion and have common objectives.

ELIGIBILITY CRITERIA
Participants and Target condition
People of any age with a diagnosis of diabetes either type I or type II

Types of Interventions:
Simple interventions such as insoles or bespoke footwear, education packages tailored for patients or health care professionals or complex interventions such as care from a specialist multidisciplinary team, used alone or in combination will be considered for inclusion in the review.
Types of comparisons
We will include simple or complex interventions used alone or in combination and standard care comparators.
Types of outcomes
A foot ulcer has been defined as a full thickness skin defect that requires more than 14 days to heal. (27)

Primary outcome
Incident primary and recurrent foot ulcers reported as binary outcomes (present/absent)

- Absolute numbers of incident ulcers
- Absolute numbers of recurring ulcers

Secondary outcomes
- Mortality
- Amputation
- Gangrene
- Infection
- Adverse events

- Harms
- Time to event
- Patient health related Quality of Life (EQ-5D, SF12, or SF6)

Types of Studies

1. Cochrane systematic reviews of RCTs of simple interventions
2. Cochrane systematic reviews of RCTs and quasi experimental designs (interrupted time series, before and after designs) of complex interventions

We will also consider non Cochrane reviews for inclusion in the overview where they have employed a clear systematic approach, have a detailed search strategy, have included only RCTs have eligible criteria relevant to our research objective, and include an assessment of the quality of the methodological elements of the included trials with a narrative synthesis and/or meta-analysis).

3. Non-Cochrane systematic reviews of RCTs of simple interventions
4. Non-Cochrane systematic reviews of RCTs of complex interventions
5. Mixed treatment comparison meta-analysis (network meta-analyses (NMA)) where these were performed as part of a systematic review of RCTs.

The Search Strategy

We will search for eligible Cochrane and non-Cochrane systematic reviews of RCTs of interventions and mixed treatment comparisons (NMAs) using the search strategy adapted from a design by the Centre for Reviews and Dissemination (CRD) at the University of York. (Appendix) Relevant reviews will be identified through searching a range of electronic databases including; The Cochrane CENTRAL register of controlled trials; The Database of Abstracts of Reviews of Effects (DARE) in the Cochrane Library; The Cochrane Library of systematic reviews; OVID MEDLINE; OVID EMBASE. Systematic reviews in progress will be identified via the PROSPERO database at CRD and we will search for a published protocol or completed review for any titles we identify. Contact will be made with the authors of these *in progress* reviews to identify reviews which may be close to publication. MEDLINE searches will be adapted for EMBASE. We will not restrict searches by language, date of publication or study setting. A search of economic literature will also be conducted to inform the development of the economic model; we will search MEDLINE, EMBASE, the HTA database and the CEA Registry for relevant studies containing economic models for the management of relevant to diabetic foot care.

Data collection

Two reviewers will screen review titles and abstracts to identify potentially relevant literature. They will then screen the full text of reviews deemed to be potentially relevant. Disagreement will be resolved by discussion with a third author. Data will be extracted into a review-specific data extraction tool by a lead reviewer and checked by a second who will be unaware of the findings of the lead reviewer.

Criteria and methods used to assess the methodological quality of the included trials

We will perform an assessment of the quality of reporting of the systematic reviews using the assessment of multiple systematic reviews (AMSTAR) instrument (28). We will also report the risk of bias tables pertaining to individual RCTs where these are reported within systematic reviews.

Presentation of the findings of the overview.

We will include a description of included reviews in which we will describe the methods used and present the characteristics of each review, the population, interventions, comparisons and outcomes evaluated therein. Where these differ, between reviews they will be noted. For each systematic review included in the overview we will present all estimates of effect reported in the included RCTs including any pooled estimates of effect.

Statistical analysis

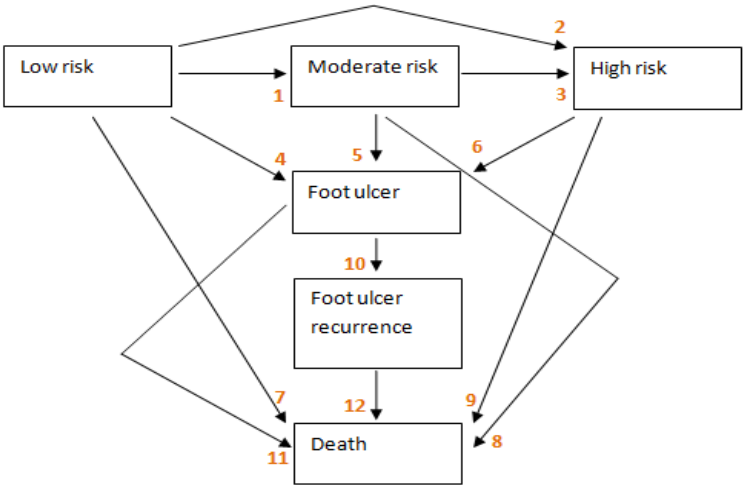
Firstly, frequentist, pairwise meta-analytical approaches will be conducted and data analysed on an intention to treat basis. Studies will be weighted according to the Mantel-Haenszel method for the dichotomous primary outcome of the overview; foot ulceration and we will use the inverse variance method for outcomes with continuous data. Heterogeneity will be assessed using the I^2statistic. We will use a fixed effect model when I^2 is less than 30% and a random effects model where heterogeneity exceeds 30%. We intend to prioritise evidence from direct, head-to-head comparisons of alternative interventions from RCTs over evidence from indirect estimates, where these data exist. Where no direct comparisons exist, we will consider undertaking a Bayesian Network Meta-Analysis (NMA) to allow the comparison of the relative effectiveness of all included

interventions. We will then evaluate whether there is inconsistency between the direct and indirect evidence by comparing the pooled estimates of each. The posterior parameters will be calculated using Markov Chain Monte Carlo (MCMC) methods. Non-informative uniform and normal prior distributions will be performed to fit the NMA model. We will automatically generate a starting value which will be used to fit the model. To rank the treatments we will use the surface under the cumulative ranking probabilities (SUCRA) to indicate which treatment is best. The robustness of the model will be tested by calculating the posterior mean residual deviance. To examine the effects of heterogeneity on patient characteristics such as baseline risk of foot ulceration we may use meta-regression techniques.

RESEARCH QUESTION 2. What are the likely clinical and cost effectiveness of alternative strategies? Objective IV; A decision analytic model

We will construct a decision analytical economic model incorporating the evidence based clinical pathway identified by the research objective i, ii and iii. The economic model will include the expected costs effects and cost effectiveness of the evidence based pathway and those recommended in the UK clinical guidelines.

Decision model:



Model structure

In this illustrative model, type I and II diabetic patients start in either the 'Low risk', 'Moderate risk' or 'High risk' states. The proportion of the cohort in each of those starting states is influenced by whether ulcer risk is assessed by the PODUS CPR or NICE/SIGN approach. Over time, patients can transit between the three risk states and we will estimate the probabilities of doing so from the PODUS dataset. The probabilities of transitions 4, 5, and 6 will be influenced by preventive treatment used, monitoring frequency used and individual patient characteristics. The pooled relative treatment effects from the overview review of the evidence of effectiveness will be applied to calculate different transition probabilities for all preventive treatment options. The probabilities of transitions 7, 8, and 9 will be influenced by individual patient characteristics. Time-to-death will be analysed by linking the Tayside PODUS cohort patients via their CHI number (10) to the SCI Diabetes routinely collected dataset. The probabilities of transition 10 will be influenced by preventive treatment used. Finally, for transitions 11 and 12 we will link all PODUS Tayside patients CHI numbers to routine outpatient and hospital data from Information Statistics Division (ISD) in Scotland to model the transition probabilities by age and sex.

Measuring effectiveness

In the economic model, effectiveness will be measured by quality adjusted life years (QALYs) and a lifetime time horizon will be used. (30) For estimating life years the PODUS Tayside data will be linked to SCI Diabetes death records to extend the observed follow-up period. Even so, parametric survival analysis will be employed to extrapolate beyond observed time points. For quality adjustments, we will estimate dis-utility for being in the different states of our model from the existing literature. Further, if we obtain dis-utility estimates for events following foot ulceration that require outpatient visit/hospitalisation (e.g. amputation) then again by linking to SCI Diabetes we can combine those estimates with the probability of those events occurring as part of our QALY calculations.

Measuring costs

Relevant costs which will be identified and measured include – costs of appointment when risk is assessed preventive treatment costs, related drug prescriptions, primary care/outpatient/hospital costs. Using the SCI DC data for patients consented to NHS Tayside cohort studies we will be able to compare certain costs pre- and post-foot ulcer events to help attribute costs to the event. Another important data source will be the NICE costing report on diabetic foot problems (31).

Cost-effectiveness analysis
The costs and effects will be measured for each potential clinical pathway (e.g. patient education intervention, monitored every 6 months). Where possible, regression models will be used to account for differences in patient characteristics and for extrapolation purposes before estimating average costs and effects for each clinical pathway. These results will be combined into incremental cost-effectiveness ratios (ICERs) to produce base case results. To address the uncertainty in the cost-effectiveness analysis, probabilistic sensitivity analysis (PSA) will be employed. Appropriate probability distributions will be assigned to each model parameter (e.g. hazard ratios for different monitoring frequencies, hazard ratios for preventive treatment effects, shape parameters from parametric survival models, etc.). PSA results will be presented in cost-effectiveness plane graphs and decision uncertainty will be expressed using cost-effectiveness acceptability curves.

RESEARCH QUESTION 3
OBJECTIVE V; THE VALUE OF INFORMATION ANALYSIS
It is likely that the level of decision uncertainty identified by the PSA results will be high. We anticipate that this will mostly be due to the weak evidence on effectiveness we expect to find from our literature review (e.g. effect sizes with large CIs due to small sample size, high risk of bias, high levels of clinical heterogeneity). Therefore, we will conduct a Value of Information (VOI) analysis to determine the value to society associated with the collection of further information on the effectiveness, costs and cost-effectiveness of alternative clinical pathway strategies. The VOI analysis will help us identify whether (and what type of) new evidence is required to support a policy decision to adopt a particular clinical pathway.

In order to establish whether future research is worthwhile we will calculate the expected value of perfect information (EVPI), which is the difference in net benefit between our current information (evidence) and perfect information (i.e. no uncertainty), and the EVPI for the population summed across the diabetic population and over a period where we expect the clinical pathway to remain the "gold standard". If the EVPI for the population is greater than the costs of carrying out the additional research then to carry out such research is potentially cost-effective. For determining what type of new evidence would be most valuable to know we can calculate the expected value of perfect information for parameters of interest (EVPPI). Likely parameters in our EVPPI analysis will be effect size for effectiveness, probability of developing foot ulcer and monitoring frequency.

If differences in net benefit can be assumed to be normally distributed then the VOI analyses will be undertaken using parametric approaches. If not, which is more likely, non-parametric simulation approaches will be undertaken.

ETHICAL APPROVAL
We are already in possession of foot ulcer events -with dates- to populate our economic model with data from people who have received a foot risk assessment (PODUS data set) so we can calculate the optimal monitoring frequency for risk assessment intervals. However, we will increase the statistical power of our analysis by undertaking a long-term follow up of patients who participated in our earlier cohort study. The results of this earlier cohort study were published in 2011. (10). We have confirmation from the podiatry manager from NHS Tayside that access to patients' hand-held podiatry notes will be granted to NHS Tayside investigator for the purpose of ascertaining outcomes. This long-term follow up will require both ethical and R&D approval.
We obtained ethical and R&D approval for the original cohort study (10) [favourable opinion obtained 23/02/2005, REC reference number 04/S1401/197; R&D project ID 2004DM04]. We remain in possession of all study patient's signed consent forms (n=1192) in which they indicate that they agree that their "... records in this research and supporting medical records be made available for inspection by monitors from NHS Tayside".. For time to death data we intend to seek Caldicott approval from NHS Tayside to collect these data from SCI diabetes for NHS Tayside patients who gave consent to participate. in our cohort study (10)

EXPERTISE
Together the applicants possess the expertise required to conduct all aspects of this project.

Dr Fay Crawford is the Senior Research Advisor for NHS Fife and an honorary fellow at the University of Edinburgh. A podiatrist and health services researcher she has undertaken many systematic reviews, evidence syntheses and primary studies across a range of clinical areas.
Dr John Chalmers is a Consultant diabetologist and the clinical lead for the Managed Clinical Network in NHS Fife. His area of specialist clinical practice includes the screening and risk assessments for the complications of diabetes.

Dr Francesca Chappell is a Medical Statistician at the University of Edinburgh whose area of expertise mostly pertains to diagnostic test accuracy and prognostic studies. She had day-to-day responsibility for the meta-analysis of the development of the PODUS dataset and prognostic model.

Professor Richard Riley is a Professor of Biostatistics at Keele University, His role focuses on statistical and methodological research for prognosis and meta-analysis, and supports clinical projects in these areas. He will acts as advisor to Dr Chappell during our research project.

Dr James Lewsey is a Medical Statistician at the University of Glasgow working in a Health Economics and HTA unit. As well as statistical expertise, he has experience in developing decision analytic models and work he has been involved in is informing SIGN guidelines on cardiovascular risk and with Professor Hawkins designed the health economics section of this bid.

Ms Karen Gray is a diabetes research nurse in the R&D department of NHS Fife. In addition to her undergraduate degree in nursing she has a post-graduate degree in Law (LLM) and is familiar with the laws pertaining to the use of patient data in medical research.

Professor Neil Hawkins is a professor of health economics at the Health Economics Health Technology Assessment (HEATA) team at the University of Glasgow. Over the last ten years, Neil has focused on health technology assessment, specializing in evidence synthesis and decision-analytic modeling.

Ms Angela Green is the principal diabetes podiatrist for NHS Fife. She has worked on Scottish government funded projects to improve podiatry service delivery for people with diabetes in the NHS.

Professor Graham Leese is Professor of diabetes and endocrinology in NHS Tayside. He is the chair of the diabetes Foot Action Group, the activities of which inform the SCI Diabetes foot screening tool (a computerise decision support tool).

Professor Julie Brittenden is Professor of vascular surgery in the Institute of Cardiovascular and Medical Sciences. She has experience of conducting HTA-funded research and has worked with Drs Chappell and Crawford on the Cochrane review of the diagnostic test accuracy of the ankle brachial index test for peripheral arterial disease, which is in the final stages of preparation. She is a member of the SIGN guideline committee on peripheral arterial disease.

Mr William Morrison is our public partner. He has participated in several RCTs evaluating various interventions for the management of diabetes and is pleased to advise the team about aspects of foot health, foot risk assessments and service delivery matter to him and others who receive NHS care. Mr William Morrison has agreed to work with us to help ensure our research is grounded in patient values, is considerate of patient perspectives and patient-centred concerns. Although it is not always possible to extract outcomes which are directly relevant to patients from primary studies included in research using data already in existence and systematic reviews, we will incorporate the outcomes suggested by the study services user in to the research protocol and where these outcomes are reported in published reports of primary research, will be extracted and used in the evidence synthesis. When these data are not reported we will include Mr Morris' suggestions in the Recommendations for Future Research section of the final report. We have included travelling and subsistence costs to support his attendance at the steering committee meetings and relevant local meetings of the applicants. The applicants will also support his involvement when technical aspects of the research need to be explained.

Professor David Weller is Professor of Primary Care Medicine and Head of the Centre for Population Health Sciences at the University of Edinburgh. He has led research projects to evaluate the National Screening Programme for colorectal cancer and is a practicing General Practitioner. He will provide institutional support for the research team at UoE and bring his perspective as a GP to the whole team.

Public Involvement

The team recognise the value and importance of involving the public in research and have experienced benefits from involving consumers in their research and have examples of the positive influence. We have the benefit of a public partner with experience of diabetes research: He has contributed to the application by reviewing it prior to submission

References

1. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet. 2005;366(9498):1719-24.
2. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation. Basis for prevention. Diabetes Care. 1990;13(5):513-21.
3. Scottish Diabetes Survey Monitoring Group. Scottish Diabetes Survey 2014. Available from: http://www.diabetesinscotland.org.uk/Publications.aspx. [accessed 17/01/2016].
4. Kerr M. footcare for people with diabetes. The economic case for change. March 2012. NHS www.diabetes.org.uk [accessed 19/01/2016]
5. Holman N, Young RJ, Jeffcoate WJ. Variation in the recorded incidence of amputation of the lower limb in England. Diabetologia. 2012;55(7):1919-25.
6. Walsh JW, Hoffstad OJ, Sullivan MO, Margolis DJ. Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom. Diabetic Medicine. 2016:DOI 10.1111/dme 13054.
7. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Risk stratification systems for diabetic foot ulcers: a systematic review. Diabetologia 2011;54(5):1190-9.
8. National Institute for Health and Care excellence (NICE Diabetic foot problems prevention and management NG19 August 2015. http://www.nice.org.uk/guidance/ng19 [Accessed 17/01/2016].
9. Management of diabetes: A National Clinical Guideline. Scottish Intercollegiate Guidelines Network (SIGN) 116; 2010. Available from: http://www.sign.ac.uk/pdf/sign116.pdf [accessed 17/01/2016].
10. Crawford F, McCowan C, Dimitrov B, Woodburn J, Wylie G, Booth E, Leese G, Bekker H, Kleijnen J, Fahey T. The risk of foot ulceration in people with diabetes screened in community settings: findings from a cohort study *QJM An International Journal of Medicine* 2011; 104(5): 403-10. E-Pub; 23rd December 2010
11. Kastenbauer T, Sauseng S, Sokol G, Auinger M, Irsigler K. A prospective study of predictors for foot ulceration in type 2 diabetes. Journal of the American Podiatric Medical Association. 2001;91(7):343-50.
12. Young MJ, McCardle JE, Randall LE, Barclay JI. Improved survival of diabetic foot ulcer patients 1995-2008: possible impact of aggressive cardiovascular risk management.) Diabetes Care. 2008;31(11):2143-7.
13. Pham H, Armstrong, Harvey C, et al. Screening techniques to identify people at high risk of foot ulceration. Diabetes care 2001;24:1442-7.
14. Rith-Najarian SJ, Stoluski T, Godhes DM. Identifying patients at high risk of amputation in a primary heath care setting. A prospective evaluation of simple screening criteria. Diabetes care; 1991;15:1386-9
15. Monami M, Vivareli M, Desideri CM, Colombi C, et al. Pulse pressure and prediction of foot ulcers intype 2 diabetes. Diabetes Care 2009;32:897-9.
16. Jeffcoate WJ. Stratification of foot risk predicts the incidence of new foot disease, but do we yet know that the adoption of routine screening reduces it? Diabetologia. 2011;54(5):991-3
17. Leese GP, Reid F, Green V, McAlpine R, Cunningham S, Emslie-Smith AM, et al. Stratification of foot ulcer risk in patients with diabetes: a population-based study. International Journal of Clinical Practice. 2006;60(5):541-5.
18. Crawford F, Cezard G, Chappell F, Murray GD, Price J, Simpson C, Sheikh A, Stansby G, Young M. A systematic review and meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulceration (PODUS). Health Technology Assessment 2015;19 (57).
19. Hoogeveen RC, Dorresteijn JAN, Kriegsman DMW, Valk GD. Complex interventions for preventing diabetic foot ulceration. Cochrane Database of Systematic Reviews 2015; Issue 8 DOI: 10.1002/14651858.CD007610.pub3.

20. Dorresteijn JAN, Kreigsman DMV, Assendelft WJJ, Valk GD, Patient education for preventing diabetic foot ulceration. Cochrane data base of systematic reviews 2014; Issue 2, Art No CD 001488, DOI 10.1002/14651858.
21. Mason J, O'Keeffe C, McIntosh A, Hutchinson A, Booth A, Young RJ. A systematic review of foot ulcer in patients with Type 2 diabetes mellitus. I: prevention. Diabetic Medicine. 1999;16(10):801-12.
22. Crawford F. How can we best prevent new foot ulceration in diabetes? *BMJ.* 2008;337:a123448
23. Steyerberg EW. Validation of prediction models. In Clinical Prediction Models. 2008.
24. Crawford F, Cezard G, Chappell F, Murray GD, Price J, Simpson C, Sheikh A, Stansby G, Young M. A systematic review and meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulceration (PODUS). Health Technology Assessment 2015;19 (57).
25. Becker LA, Oxman AD. Overview of reviews. Chapter 22 In The Cochrane Handbook for systematic reviews of interventions eds Higgins J, Green SWiley-Blackwell,2009.
26. Wu et al Dressing for treating people with diabetes an overview of systematic reviews. CochraneDatabase of systematic reviews 2015, issue 7.
27. Boyko EJ, Ahroni JH, Cohen V, Nelson KM, Heagerty PJ. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic Foot Study. Diabetes Care. 2006;29(6):1202-7.
28. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andresson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of stystemetic reviews. BMC Medicla Research Methodology 2007;15 (7):10.
29. Mills EJ, Ioannidis JPA, Thorlund K, Schunemann HJ, Puhen MA, Guyatt GH. How to Use an Article Reporting a Multiple Treatment Comparison Meta-analysis. JAMA 2012;308(12);1246-1253. Doi: 10.1001/2012 jama 11228.
30. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. Article PMG 9. April 2013. https://www.nice.org.uk/article/pmg9/chapter/glossary#cost-effectiveness-analysis.[Accessed 17/01/2016].
31. Putting NICE guidance into practice. Costing report implementing the NICE guideline on diabetic foot problems (NG19) https://www.nice.org.uk/guidance/ng19/resources/costing-report-544624525 Accessed 12th May 2016.

Acknowledgement

This project was funded by the National Institute for Health Research Health Technology Assessment (project number 15/171/01)

NHS
National Institute for Health Research

Appendices

strategy adapted from CRD strategy for reviews and network meta analyses.(28)

The Cochrane Central Register of Controlled Trials
(CENTRAL; *The Cochrane Library* 2016,);
2. Database of Abstracts of Reviews of Effects (DARE; *The*
Cochrane Library 2016,);
3. Ovid MEDLINE (1950 to 20 April 2016);
4. Ovid MEDLINE (In-Process & Other Non-Indexed
Citations, 20 April 2016);
5. Ovid EMBASE (1980 to 20 April 2016)

We used the following search strategy to identify non-Cochrane systematic reviews in MEDLINE;

Ovid Technologies, Inc. Email Service

Search for: 18 and 60
Results: 1

Database: Ovid MEDLINE(R) <1946 to April Week 4 2016> Search Strategy:

---

1 exp Foot Orthoses/ (392)
2 exp Shoes/ (5243)
3 exp health education/ (144988)
4 exp primary health care/ (114301)
5 exp Foot/ or exp Diabetic Foot/ or exp Podiatry/ or exp Foot Diseases/ (65867)
6 exp Diabetic Neuropathies/ or exp Diabetic Foot/ or exp Foot Ulcer/ (19807)
7 exp Emollients/tu [Therapeutic Use] (1038)
8 exp shoes/ (5243)
9 (insoles* or footwear* or education* or specialist care* or multi disciplinary team* or routine podiatry care* or
offloading* or emollients* or shoes*).tw. (361314)
10 or/1-9 (630560)
11 exp Diabetic Neuropathies/ or exp Foot Diseases/ or exp Diabetes Mellitus/ or exp Foot/ or exp Skin Ulcer/ or exp
Bacterial Infections/ or exp Adult/ or exp Middle Aged/ or exp Foot Ulcer/ or exp Ultrasonography/ or exp Aged/
(6897694)
12 exp Ischemia/ or exp Diabetic Neuropathies/ or exp Aged/ or exp Diabetic Angiopathies/ or exp Skin Ulcer/ or exp
Diabetes Complications/ or exp Foot/ or exp Foot Diseases/ or exp Diabetic Foot/ or exp Adult/ or exp Middle Aged/
(6140023)
13 (diabet* adj3 ulcer*).tw. (3115)
14 (diabet* adj3 (foot or feet)).tw. (5722)
15 (diabet* adj3 wound*).tw. (1692)
16 (diabet* adj3 amputat*).tw. (724)
17 or/11-16 (6926557)
18 10 and 17 (298372)
19 systematic* review*.tw. (66545)
20 meta-analysis as topic/ (14831)
21 (meta-analytic* or meta-analysis or metanalysis or meta analysis or metaanalysis or meta synthesis or meta
synthesis or meta-regression or meta regression or meta regression).tw. (67302)
22 (synthes* adj3 literature).tw. (1493)
23 (synthes* adj3 evidence).tw. (4504)
24 (integrative review or data synthesis).tw. (8580)

25 (research synthesis or narrative synthesis).tw. (892)
26 (systematic study or systematic studies).tw. (6973)
27 (systematic comparison* or systematic overview*).tw. (1908)
28 ((evidence based or comprehensive or critical or quantitative or structured) adj review).tw. (20149)
29 (realist adj (review or synthesis)).tw. (122)
30 or/19-29 (157335)
31 review.pt. (2043551)
32 (medline or pubmed or embase or cinahl or psyc?lit or psyc?info).ab. (92204)
33 ((literature or database* or bibliographic or electronic or computeri?ed or internet) adj3 search*).tw. (61773)
34 (electronic adj3 database*).tw. (12330)
35 included studies.ab. (8641)
36 (inclusion adj3 studies).ab. (7361)
37 ((inclusion or selection or predefined or predetermined) adj criteria).ab. (59686)
38 (assess* adj3 (quality or validity)).ab. (44185)
39 (select* adj3 (study or studies)).ab. (39840)
40 (data adj3 extract*).ab. (31963)
41 extracted data.ab. (7856)
42 (data adj3 abstraction).ab. (909)
43 published intervention*.ab. (113)
44 ((study or studies) adj2 evaluat*).ab. (112385)
45 (intervention* adj2 evaluat*).ab. (6486)
46 (confidence interval* or heterogeneity or pooled or pooling or odds ratio*).ab. (446085)
47 (Jadad or coding).ab. (124545)
48 or/32-47 (858808)
49 31 and 48 (142144)
50 review.ti. (268679)
51 48 and 50 (54347)
52 (review* adj4 (papers or trials or studies or evidence or intervention* or evaluation*)).tw. (108096)
53 30 or 49 or 51 or 52 (305482)
54 letter.pt. (882264)
55 editorial.pt. (377279)
56 comment.pt. (620348)
57 or/54-56 (1389907)
58 53 not 57 (297721)
59 exp animals/ not humans/ (4236009)
60 58 not 59 (287436)
61 18 and 60 (4916)