National Institute for Health and Care Excellence

Final

Diabetic foot problems: prevention and management

[B] Evidence reviews for risk assessment models and tools for predicting the development of diabetic foot problems and foot review frequency

NICE guideline NG19

Evidence reviews underpinning recommendations 1.3.4, 1.3.6, 1.3.7, 1.3.11 and research recommendations in the NICE guideline

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1.1 Review question

In people with diabetes which risk assessment models/tools better predicts the development of diabetic foot problems?

1.1.1 Introduction

Foot complications are common in people with diabetes. It is estimated that 10% of people with diabetes will have a diabetic foot ulcer at some point in their lives. Diabetes is also the most common cause of non-traumatic limb amputation, with diabetic foot ulcers preceding more than 80% of amputations in people with diabetes. After a first amputation, people with diabetes are twice as likely to have a subsequent amputation as people without diabetes. Mortality rates after diabetic foot ulceration and amputation are high, with around 50% of people dying within 5 years of developing a diabetic foot ulcer and up to 70% dying within 5 years of having an amputation.

The NICE guideline on diabetic foot problems: prevention and management (NICE guideline NG19) was reviewed by the NICE surveillance team in 2021 to examine the impact of a published health technology assessment (HTA) on risk assessments and structured care interventions for the prevention of foot ulceration in diabetes: development and validation of a prognostic model (Crawford et al. 2020). This new evidence indicated that a newly developed and validated clinical prediction rule, the PODUS CPR (Prediction Of Diabetic foot UlcerationS), uses fewer clinical indicators and a more simple calculation than the currently recommended modified SIGN (Scottish Intercollegiate Guidelines Network) risk assessment tool and may represent an opportunity to simplify practice and reduce costs.

The 2015 version of the guideline recommended that practitioners use a range of indicators to stratify people into low risk, moderate risk, high risk, and active problem groups. These indicators include deformity, neuropathy, peripheral arterial disease, and previous ulceration or amputation. They are based on the SIGN tool, with the addition of an item assessing for the presence of renal disease. These recommendations were based on 4 studies and committee consensus.

The new evidence suggested that just 3 key clinical indicators could be used to assess a patients' risk of developing a foot ulcer: sensitivity to a 10-g monofilament, presence or absence of pedal pulses, and whether there is a history of previous ulcer or lower extremity amputation. The authors of the HTA argued that these risk factors are relatively quick and simple to assess during foot examinations, do not require complex or expensive equipment, and could simplify current approaches to assessing and calculating risk. The NICE surveillance team concluded that this new evidence is a sufficient basis for an expert committee to consider the impact of the new PODUS CPR on risk assessment approaches and subsequent diabetic foot review frequency recommendations.

The aim of this review is to assess which risk stratification models/tools perform better in indicating risk of diabetic foot problems in people with type 1 or type 2 diabetes. This review identified prospective and retrospective cohort studies that fulfilled the conditions specified in Table 1. See Appendix A for full details of the review protocol.

1.1.2 Summary of the protocol

Table 1: PICO table for risk stratification of diabetic foot problems

Population	People with type 1 or type 2 diabetes
Intervention	Risk stratification models/tools for predicting the development of diabetic foot problems. Examples: • PODUS CPR 2020 • SIGN risk stratification tool • Seattle risk score • American Diabetes Association • University of Texas Foot Risk System • International Working Group on the Diabetic Foot risk classification systems
Reference standard	Diagnosis of diabetic foot ulcer
Outcome measures	For each outcome, metric measures will be reported where available, for example: • Odds ratios/hazard ratios • Model fit statistics (for example R^2, Brier score) • Discrimination (for example C-statistic, area under ROC curve) • Calibration (for example calibration slope)

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods section in appendix K.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

The review protocol specified that, where possible, subgroup analyses would be conducted for age, sex, ethnicity, duration of diabetes, diabetes type (type 1 or type 2), and presence of renal disease. However, these subgroups could not be analysed due to insufficient data.

As no published guidance on applying GRADE to prognostic reviews exists, to assess the quality of evidence a modified approach using the GRADE framework was applied. The committee did not define a clinical decision threshold prospectively, therefore the line of no effect was used as the clinical decision threshold for the purpose of rating imprecision in GRADE. For further discussion of GRADE assessments for imprecision for likelihood ratios, c-statistics and incidence rates, see the methods section in appendix K.

1.1.3.1 Protocol deviations

The protocol did not list sensitivity, specificity and likelihood ratios as included outcome measures, largely because this was a prognostic review and not a diagnostic accuracy review. However, these outcome measures were reported in several of the included studies, and due to the lack of evidence and lack of overlap in other outcome measures reported across the studies, a decision was made to report this data.

1.1.4 Prognostic evidence

1.1.4.1 Identification of evidence

A joint systematic search was carried out to identify studies specified for this evidence review, and a linked evidence review for studies assessing the frequency of diabetic foot reviews (for details, see section 2.1 of this document). See Appendix B for the literature search strategy. In total, 6799 references were identified and screened at title and abstract level, of which 76 papers were identified as potential includes and ordered for full-text screening. All full texts were reviewed against the inclusion criteria detailed in the respective protocols, of which 4 papers reporting on 3 studies met the inclusion criteria for the evidence review on risk assessment tools, and 2 papers reporting on 1 study met the inclusion criteria for the evidence review on frequency of foot review. 1 paper was included in both reviews. 71 papers were excluded. The evidence study selection process is presented as a diagram in Appendix C.

1.1.4.2 Included studies

Of the 4 papers included in the risk assessment review, 2 were prospective cohort studies, 1 was a retrospective cohort study, and 1 was a secondary publication of the Crawford (2020) prospective cohort study which was used for supplementary information only. Two studies reported on the development and validation of new models for assessing risk of developing a diabetic foot ulcer, but each study reported on a different model; one was the Chen 2021 9-item risk prediction model for DFU, and the other was the PODUS 3-item clinical prediction rule. A third study validated 6 different diabetic foot risk assessment tools in a multicentre sample from community and hospital settings. See Table 2 for a summary of studies. See section 3.7.1 References for a list of included references.

1.1.4.3 Excluded studies

See Appendix I for a list of excluded studies with reasons for exclusion.

1.1.5 Summary of studies included the prognostic evidence

Table 2: Summary of included studies

Study	Location and setting	Population	Risk assessment model	Outcomes
Chen 2021 Retrospective cohort study	China Hospital setting	Validation cohort: patients with type 2 diabetes (n = 465)	Chen 2021 risk prediction model for diabetic foot ulcer	- Sensitivity and specificity - C-statistic - Cumulative incidence risk of each group using Kaplan-Meier survival analysis - RR of developing diabetic foot ulcer for each risk group compared to the low-risk group
Crawford 2020 Prospective cohort study	Development cohort: 2 studies set in the community in the UK and 2 hospital based studies, 1 in Portugal and 1 in the USA. Validation cohort: UK Community setting – community and hospital foot clinics	Development cohort: patients with diabetes aged ≥18 years (n = 8404) Validation cohort: patients with diabetes aged ≥18 years (n = 3412)	PODUS CPR	- C-statistic - Intercept and slope of calibration plot - Population-based probability of ulcer at 2-years
Monteiro-Soares 2017[a] Prospective cohort study	Portugal Community and hospital settings	Patients with diabetes (n = 446)	- ADA classification - IWGDF classification - SIGN classification - Seattle Risk Score[b] - UTFRS	- Sensitivity and specificity - Positive and negative likelihood ratios - C-statistic

Prediction of Diabetic Foot Ulcerations (PODUS); Clinical Prediction Rule (CPR); American Diabetes Association (ADA); International Working Group on the Diabetic Foot (IWGDF); Scottish Intercollegiate Grouping Network (SIGN); University of Texas Foot Risk System (UTFRS)

[a] This paper reports results for the PODUS but this was the PODUS prognostic model reported in Crawford 2015 and not the PODUS CPR reported in Crawford 2020, so results for this tool were not extracted.

[b] The paper reports results for the original Seattle Risk Score and the refined Seattle Risk Score. As the refined scoring system was shown to better predict development of DFU in previous model validation studies, only results for the refined version are used in this review.

See appendix D for full evidence tables.

1.1.6 Summary of the prognostic evidence

1.1.6.1 Model summaries

Chen 2021 model

The model reported by Chen was developed using a derivation cohort of 46,521 patients with type 2 diabetes from America (USA, Brazil, Canada), Europe (UK, Denmark, Norway, Italy), Asia (China, South Korea, Iran, Japan), Australia, and Ethiopia. The model is based on a systematic review and meta-analysis of risk factors for DFU and is designed to use 9 commonly assessed variables to help clinicians identify patients at greatest risk of developing diabetic foot complications. Each of the 9 items has an associated risk score and clinicians are required to calculate a total score, as shown in Table 3. Scores can range from 0 to 80 with higher scores indicating a greater risk and suggested risk groupings of low risk (scores <28.5), low-intermediate risk (scores 29-46.5), high-intermediate risk (scores 47-57.5) and high risk (scores 58-80).

Table 3: Chen 2021 risk score model of DFU prediction

Risk factor	Risk score
Sex	
Female	0
Male	6
BMI (Kg/m^2)	
< 24	0
24.00-27.99	4
≥28	8
HbA1c (% [mmol/ mol])	
< 7.0 [<53]	0
7.0-7.9 [53-63]	2
8.0-8.9 [64-74]	4
≥ 9.0 [≥75]	6
Smoker[a]	
Yes	6
No	0
Diabetic nephropathy[b]	
Yes	11
No	0
Diabetic retinopathy[c]	
Yes	11
No	0
Diabetic peripheral neuropathy[d]	
Yes	10
No	0
Intermittent claudication[e]	
Yes	13
No	0

Risk factor	Risk score
Foot care[f]	
Yes	0
No	9

[a] *Smoking defined as total ≥100 cigarettes in their lifetime, regardless of current smoking or not*
[b] *Diabetic nephropathy defined as an eGFR < 60 mL/min/1.73m^2 and/or severe albuminuria (ACR > 300 mg/mmol or > 3000 mg/g) caused by diabetes mellitus for > 3 months*
[c] *Confirmed by ophthalmoscopy*
[d] *Confirmed using a combination of symptoms, signs and nerve conduction function consistent with neuropathy in the 2010 Toronto consensus*
[e] *Walking pain or 'limping' caused by peripheral arterial disease*
[f] *Considered to be regular foot washing, daily foot self-examination, not barefoot walking, wearing slippers and loose socks, at least once a year foot specialist examination*

PODUS Clinical Prediction Rule

The PODUS (Prediction of Diabetic foot Ulcerations) project used individual participant data from a large international dataset in a systematic review and meta-analysis to identify predictors of DFU. They used this to develop a prognostic model that was subsequently converted into a clinical prediction rule (CPR) comprising 3 predictors: insensitivity to a 10g monofilament, an absent pedal pulse in either foot, and previous history of ulceration or amputation. This results in a CPR that gives scores from 0 to 4, with higher scores indicating greater risk of developing DFU and the following risk groups: low risk (score of 0 or 1), moderate risk (score of 2), or high risk (score of 3 or 4). See Table 4 for details of the scoring system. The authors highlight that the 3 predictors are easy to collect during patient foot examinations and are usually recorded in health records. The CPR requires very little calculation by the end-user and provides a simple way of quantifying a person's risk of foot ulceration over a 2-year timescale (via the person-specific probability of foot ulceration data provided in section 1.1.6.2.4 of this review).

Table 4: PODUS Clinical Prediction Rule

Risk factor	Risk score
Test with 10-g monofilament	
Insensitive at any site	1
Sensitive at all sites	0
Check pedal pules	
Any pulse missing	1
Four pulses present	0
Has there been an ulcer or amputation previously?	
Any ulcer or amputation	2
No ulcer or amputation	0
Total score	Range 0-4

SIGN

This stratification system was developed based on consensus of a multidisciplinary group of practitioners and was subsequently validated in a community-based prospective cohort study which led to slight modifications to the original format (Leese et al., 2006; Leese et al. 2011). The modified SIGN system assesses the following risk factors: foot deformity, diabetic neuropathy using 10-g monofilament, physical impairment, visual impairment, previous foot ulceration, lower extremity amputation, and peripheral vascular disease assessed using pedal pulses. Foot deformity was defined as a change in foot shape that resulted in difficulty in fitting in standard shoes. Physical impairment was defined as the patient not being able to reach their feet and visual impairment was defined as patients not being able to see their feet safely enough to cut their nails. Patients with no risk factors are classed as low risk; patients with one risk factor are classed as medium risk; and patients with two or more risk factors, or a previous history of foot ulcer or amputation are classed as high risk. These risk groups are displayed in Table 5.

Table 5: SIGN risk stratification system

Risk factor	Risk group
No DN; no PVD; no FD; no PI; and no VI	Low
DN or PVD or FD or VI or PI	Medium
History of foot ulceration or LEA or PVD and DN or one of the above, with callus or deformity	High

DN: diabetic neuropathy; PVD: peripheral vascular disease; FD: foot deformity; PI: physical impairment; VI: visual impairment; LEA: lower extremity amputation

International Working Group of the Diabetic Foot (IWGDF)

This stratification system was created through consensus by 45 expert clinicians and researchers. It has since undergone small modifications, primarily the subdivision of risk groups 2 and 3 into 2A and 2B, and 3A and 3B. The tool assesses diabetic neuropathy (assessed using a 10-g monofilament or a vibration perception threshold > 25V), peripheral vascular disease (indicated by an ankle–brachial index (ABI) inferior to 0.8 and any non-palpable pedal pulse), foot deformity, history of foot ulcer, and lower extremity amputation. The risk groups are displayed in Table 6.

Table 6: IWGDF risk stratification system

Risk factor	Risk group
No DN and no PVD	0
DN but no FD or PVD	1
DN and FD but no PVD	2A

Risk factor	Risk group
PVD	2B
History of foot ulcer	3A
History of LEA	3B

DN: diabetic neuropathy; PVD: peripheral vascular disease; FD: foot deformity; LEA: lower extremity amputation

ADA

The American Diabetes Association (ADA) system assesses variables previously shown to be related to foot ulcer development: diabetic neuropathy, peripheral vascular disease, foot deformity, and foot ulcer or amputation history. The tool initially held that anyone presenting with any of these conditions was at high risk, but subsequent modifications proposed a stratification system that graded patients across 4 risk groups by estimated cumulative risk. The risk groups are displayed in Table 7.

Table 7: ADA risk stratification system

Risk factor	Risk group
No risk factors for foot ulcer	0
DN and/or FD	1
PVD and/or DN	2
History of DFU or LEA	3

DN: Diabetic neuropathy; PVD: peripheral vascular disease; FD: foot deformity; LEA: lower extremity amputation

University of Texas Foot Risk System (UTFRS)

This system assesses only three variables which the authors claim are frequently available in daily practice: diabetic neuropathy, foot deformity, and ulcer or lower extremity amputation history. Patients are categorised into one of 4 risk groups based on the presence or absence of these symptoms; see Table 8 for details of each risk group.

Table 8: UTFRS risk stratification system

Risk factor	Risk group
No DN	0

Risk factor	Risk group
DN but no FD	1
DN and FD	2
DN and FD and history of ulcer or LEA	3

DN: Diabetic neuropathy; FD: foot deformity; LEA: lower extremity amputation

Seattle Risk Score

Also known as the Boyko et al. (2006) system, this stratification system was developed in a prospective cohort study of 1285 veterans who were followed up every 12-18 months over 3 years, and subsequently externally validated in a 2010 retrospective cohort study of 360 participants followed for 25 months. Risk factors included in the original model were HbA1c, diabetic neuropathy (diagnosed using 10-g monofilament), poor vision (with respect to the patient's ability to inspect their own feet and perform regular foot care), *tinea pedis* (athlete's foot), onychomycosis (fungal nail infection), history of foot ulcer, and history of lower limb amputation. Subsequent modifications suggested inclusion of a footwear risk variable improved the accuracy of the model, so an assessment of footwear is included in the revised tool.[a] A complex risk score equation was developed from analyses of the data and based on the resultant score, patients are stratified into lowest risk, next-to-lowest risk, next-to-highest risk, and highest risk groups.[b] Analyses showed the best stratification was achieved using the following cut-off scores: under 3.87 (lowest risk); 3.87 to 5.66 (next-to-lowest risk); 5.67 to 6.81 (next-to-highest risk); above 6.81 (highest risk). Details of this system are not presented in a table because a patients' risk group depends on a score calculation with multiple possible variable combinations.

1.1.6.2 Summary of clinical findings included in the evidence review

1.1.6.2.1 Predictive accuracy measures for the development of diabetic foot ulcer (DFU)

No. studies	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95% CI)	Quality
Chen 2021 model: cut-off score of ≥ 46.5. Outcome: development of DFU					
1	465	0.769 (not reported)	0.798 (not reported)	LR+ (not reported)	Moderate[a]
				LR- (not reported)	Moderate[a]
American Diabetes Association (ADA): high risk group. Outcome: development of DFU					

[a] Patients were asked to describe their most frequently worn shoes, which was evaluated and classified: (1) as low-risk if it covered the foot adequately, had laces and was of the correct size; (2) as moderate-risk for slippers, shoes without laces or shoes made from an inappropriately soft material; and (3) as high-risk if too small, or defined as sandals or flip-flops. Patients presenting with lesions, callosities or reddened sites due directly to footwear were immediately classed as using high-risk footwear, regardless of the shoes described or worn at the appointment.

[b] Risk score equation: score=0.373× (HbA1c in %) + 0.217× (presence of visual impairment) + 2.037× (presence of previous ulcer history) + 0.593× (presence of previous amputation) + 0.637× (presence of monofilament insensitivity) − 1.256 × (presence of tinea pedis) + 0.217× (presence of onychomycosis) + 1.905× (use of moderate- or high-risk footwear).

No. studies	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95% CI)	Quality
1	446	0.72 (0.56-0.87)	0.87 (0.84-0.90)	LR+ 5.6 (4.0-7.8)	Low
				LR- 0.3 (0.2-0.6)	Very low
American Diabetes Association (ADA): high and moderate risk group. Outcome: development of DFU					
1	446	0.84 (0.72-0.97)	0.77 (0.72-0.81)	LR+ 3.6 (2.9-4.5)	Low
				LR- 0.2 (0.09-0.5)	Very low
American Diabetes Association (ADA): high, moderate and low risk group. Outcome: development of DFU					
1	446	0.94 (0.85-1.00)	0.50 (0.45-0.55)	LR+ 1.9 (1.7-2.1)	Very low
				LR- 0.1 (0.03-0.5)	Very low
IWGDF: 3A + 3B. Outcome: development of DFU					
1	446	0.72 (0.56-0.87)	0.87 (0.84-0.90)	LR+ 5.5 (4.0-7.6)	Low
				LR- 0.3 (0.2-0.6)	Very low
IWGDF: 3A + 3B + 2A + 2B. Outcome: development of DFU					
1	446	0.91 (0.81-1.00)	0.62 (0.58-0.67)	LR+ 2.4 (2.0-2.8)	Low
				LR- 0.2 (0.05-0.4)	Low
IWGDF: 3A + 3B + 2A + 2B + 1. Outcome: development of DFU					
1	446	0.94 (0.85-1.00)	0.50 (0.45-0.54)	LR+ 1.9 (1.6-2.1)	Very low
				LR- 0.2 (0.05-0.4)	Low
Seattle (refined): Highest risk. Outcome: development of DFU					
1	446	0.38 (0.17-0.59)	0.96 (0.94-0.98)	LR+ 10.2 (4.7-21.8)	Low
				LR- 0.6 (0.5-0.9)	Very low
Seattle (refined): Highest and next-to-highest. Outcome: development of DFU					
1	446	0.71 (0.52-0.91)	0.88 (0.84-0.91)	LR+ 5.8 (3.9-8.5)	Low
				LR- 0.3 (0.2-0.6)	Low
Seattle (refined): Highest and next-to-highest and next-to-lowest. Outcome: development of DFU					
1	446	0.95 (0.86-1.00)	0.36 (0.31-0.41)	LR+ 1.5 (1.3-1.7)	Low

No. studies	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95% CI)	Quality
				LR- 0.1 (0.02-0.9)	Low
SIGN: High risk. Outcome: development of DFU					
1	446	0.91 (0.81-1.00)	0.58 (0.53-0.63)	LR+ 2.2 (1.8-2.5)	Very low
				LR- 0.2 (0.05-0.5)	Very low
SIGN: High and medium risk. Outcome: development of DFU					
1	446	0.94 (0.85-1.00)	0.50 (0.45-0.54)	LR+ 1.9 (1.6-2.1)	Very low
				LR- 0.1 (0.03-0.5)	Very low
UTFRS: 3. Outcome: development of DFU					
1	446	0.31 (0.15-0.47)	0.98 (0.97-1.00)	LR+ 18.5 (7.5-45.3)	Low
				LR- 0.7 (0.6-0.9)	Low
UTFRS: 3 + 2. Outcome: development of DFU					
1	446	0.72 (0.56-0.87)	0.74 (0.70-0.79)	LR+ 2.8 (2.1-3.7)	Low
				LR- 0.4 (0.2-0.7)	Very low
UTFRS: 3 + 2 + 1. Outcome: development of DFU					
1	446	0.75 (0.60-0.90)	0.59 (0.54-0.64)	LR+ 1.8 (1.4-2.3)	Very low
				LR- 0.4 (0.2-0.8)	Very low

[a] No confidence intervals reported so not possible to assess imprecision. GRADE quality rating based on assessment of other GRADE dimensions excluding imprecision. This is discussed in more detail in the methods section in appendix L.

1.1.6.2.2 C-statistics

Risk stratification model	Study (s)	No. of participants	C-statistic (95% CI)	Quality
Chen 2021 model	Chen 2021	465	0.798 (0.738-0.858)	Low
PODUS CPR	Crawford 2020	8404	0.83 (0.79-0.87)	Moderate
ADA	Monteiro-Soares 2017	446	0.86 (0.76-0.95)	Very low
IWGDF	Monteiro-Soares 2017	446	0.86 (0.77-0.96)	Very low
Seattle Refined (continuous)	Monteiro-Soares 2017	446	0.88 (0.81-0.96)	Very low
Seattle Refined (categorical)	Monteiro-Soares 2017	446	0.84 (0.74-0.93)	Very low

Risk stratification model	Study (s)	No. of participants	C-statistic (95% CI)	Quality
SIGN	Monteiro-Soares 2017	446	0.75 (0.66-0.84)	Very low
UTFRS	Monteiro-Soares 2017	446	0.77 (0.65-0.89)	Very low

PODUS: Prediction Of Diabetic Foot Ulcerations; ADA: American Diabetes Association; IGDWF: International Working Group on the Diabetic Foot; SIGN: Scottish Intercollegiate Grouping Network; UTFRS: University of Texas Foot Risk System

1.1.6.2.3 Calibration statistics

	Effect estimate (95% CI)	Quality
Calibration slope		
PODUS CPR	1.139 (0.994 to 1.283)	High
Calibration intercept		
PODUS CPR	-0.059 (-0.431 to 0.314)	High

1.1.6.2.4 Population-based probability of ulcer at 2-years

Risk stratification group	No. of participants	Probability of ulcer at 2 years (95% CI)	Quality
PODUS CPR score 0	4646	0.024 (0.014 to 0.039)	High
PODUS CPR score 1	2406	0.060 (0.035 to 0.095)	High
PODUS CPR score 2	676	0.140 (0.085 to 0.213)	High
PODUS CPR score 3	358	0.292 (0.192 to 0.410)	High
PODUS CPR score 4	169	0.511 (0.379 to 0.641)	High

Note: Data for these analyses were based on the development cohort in Crawford 2020 and not the validation cohort

1.1.6.2.5 Risk ratios for developing DFU

Risk stratification group	Reference	No. of participants	Risk ratio (95% CI)	Quality
Chen 2021 model				
Low-intermediate risk group	Low risk group	465	1.50 (0.41 to 5.44)	Very low
Chen 2021 model				
High-intermediate risk group	Low risk group	465	17.23 (5.12 to 58.02)	Moderate
Chen 2021 model				
High risk group	Low risk group	465	21.75 (5.16 to 91.74)	Moderate

See appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix B). This search retrieved 1304 studies. Based on title and abstract screening, 1303 of the studies could confidently be excluded for this review question. One study was excluded following the full-text review since the interventions being explored were not relevant to the review question. No relevant health economic studies were included.

1.1.7.2 Excluded studies

See 0 for excluded studies and reasons for exclusion.

1.1.8 Summary of included economic evidence

No relevant health economic studies were identified to be included.

1.1.9 Economic model

Original health economic modelling was not prioritised for this review question.

2 Frequency of diabetic foot review

2.1 Review question

How often should people with diabetes who are at low risk, moderate risk, or high risk of developing a diabetic foot problem or needing an amputation be reviewed?

2.1.1 Introduction

The NICE guideline on diabetic foot problems: prevention and management (NICE guideline NG19) was reviewed by the NICE surveillance team in 2021 to examine the impact of a published health technology assessment (HTA) on risk assessments and structured care interventions for the prevention of foot ulceration in diabetes: development and validation of a prognostic model (Crawford et al. 2020). This new evidence indicated that the risk of developing a foot ulcer did not change over time for most people, and that people at low risk of developing a diabetic foot ulcer may only need to be reviewed once every 2 years instead of annually.

The 2015 guideline recommended that diabetic foot review frequencies should be as follows: annually for people who are at low risk; frequently (for example, every 3 to 6 months) for people who are at moderate risk; more frequently (for example, every 1 to 2 months) for people who are at high risk, if there is no immediate concern; and very frequently (for example, every 1 to 2 weeks) for people who are at high risk, if there is immediate concern. These recommendations were based on committee consensus only as no relevant evidence was identified.

The new evidence showed that most people's risk of developing a foot ulcer does not change over time, so the authors suggested that risk assessments may be undertaken at 2-yearly intervals for low-risk groups. It was concluded that this new evidence is a sufficient basis for an expert committee to consider the impact of the new PODUS clinical prediction rule on diabetic foot review frequency recommendations.

The aim of this review is to assess people's change in risk status over time and to determine the most effective and cost-effective review schedule frequency for the different risk categories. This review identified observational studies that fulfilled the conditions specified in Table 9. See Appendix A for full details of the review protocol.

2.1.2 Summary of the protocol

Table 9: PICO table for diabetic foot review frequency

Population	People with type 1 or type 2 diabetes
Intervention	Review schedules of varying frequency for the risk categories
Comparator	Standard care based on risk category
Outcomes	• Foot ulcer incidence (including severity) • Soft tissue infections • Osteomyelitis

	• Gangrene incidence resulting from diabetes • Amputation incidence (major and minor) • Charcot arthropathy • Critical limb ischemia / chronic limb threatening ischemia • All-cause mortality • Rates of A&E presentation / hospital admission for foot problems resulting from diabetes (Non-scheduled clinical encounters relating to diabetic foot problems)

2.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods section in appendix K.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

2.1.4 Observational evidence

2.1.4.1 Identification of evidence

A joint systematic search was carried out to identify studies specified for this evidence review, and the evidence review reported in section 1.1 of this document. See Appendix B for the literature search strategy, and section 1.1.4.1 for details of the screening process and results. For this review on the frequency of diabetic foot review, 2 papers reporting on 1 study met the inclusion criteria. The evidence study selection process is presented as a diagram in Appendix C.

2.1.4.2 Included studies

The 1 study included in this review was a retrospective cohort study of people with diabetes attending community-based foot screening and was based on routinely collected data from a national diabetes register. The study was reported primarily in a Health Technology Assessment (Crawford 2020), but additional information was contained in a secondary publication (Heggie 2020) that was used for supplementary information only. The analyses in this secondary publication were based on a sub-sample of the larger population reported in the HTA. See Table 10 for a summary of studies. See section 3.7.1 References for a list of included references.

2.1.4.3 Excluded studies

See Appendix I for a list of excluded studies with reasons for exclusion.

2.1.5 Summary of studies included the observational evidence

Table 10: Summary of included studies

Study	Location and setting	Population	Follow-up period	Outcomes
Crawford 2020 Retrospective cohort study	Fife, UK Community-based foot screening clinics	Patients with type 1 or type 2 diabetes N = 26,086	8 years	- Change in risk status over time for patients at low risk - Frequency of ulceration in each risk group by length of follow-up - Survival probabilities for time to ulceration conditional on CPR state and time to amputation conditional on CPR state (Kaplan-Meier curves)
Heggie 2020 Retrospective cohort study Secondary publication of Crawford 2020	Fife, UK Community-based foot screening clinics	Patients with type 1 or type 2 diabetes Sub-sample of population reported in Crawford 2020 N = 10,421	8 years	- Cumulative incidence of ulceration, amputation and death among low risk cohort - Person years and crude incidence rates of transition from low to moderate risk status

See appendix D for full evidence tables.

2.1.6 Summary of the observational evidence

2.1.6.1 Summary of findings included in the observational evidence review

Table 11: Change in PODUS risk status over time (first to final clinical appointment)

Risk stratification group at first visit	Risk stratification group at final visit			Total (N)
	Low	Moderate	High	
Low	23,867 (95.5%)	*639 (2.56%)*	*497 (1.99%)*	25,003
Moderate	0	452 (63.4%)	*261 (36.6%)*	713
High	0	0	370 (100%)	370
Total	23,867	1091	1128	26,086

Italicised figures indicate a change in risk category

Percentages calculated by analyst

Other analyses reported in the Crawford 2020 HTA showed that there were no participants who transitioned directly from low-risk to high-risk.

Table 12: Patterns of ulceration in each risk group by length of follow-up

Risk group	Length of follow-up (years)	New foot ulcer (n)	No new foot ulcer (n)	Total (n)
Low	≤ 1	20	704	724
	1-2	15	415	430
	2-3	3	67	70
	≥ 3	6	78	84
	Total	44	1264	1308
Moderate	≤ 1	15	76	91
	1-2	9	44	53
	2-3	1	20	21
	≥ 3	4	10	14
	Total	29	150	179
High	≤ 1	57	50	107
	1-2	25	53	78
	2-3	16	60	76
	≥ 3	17	20	37
	Total	115	183	298

Risk group	Length of follow-up (years)	New foot ulcer (n)	No new foot ulcer (n)	Total (n)

Data taken from 3 development studies included in the Crawford 2020 HTA: Crawford 2011; Monteiro-Soares 2010; and Pham 2000.

The results in Table 12 show that across the entire follow-up period, the risk categories had an overall percentage of ulceration of 3.4%, 16.2% and 38.6% for low-, medium- and high-risk groups, respectively. They also show that of the 44 patients in the low-risk group that developed a foot ulcer during the entire follow-up period, 20 of those (45%) developed a foot ulcer within the first year, and an additional 15 (34%) developed a foot ulcer between years 1 and 2.

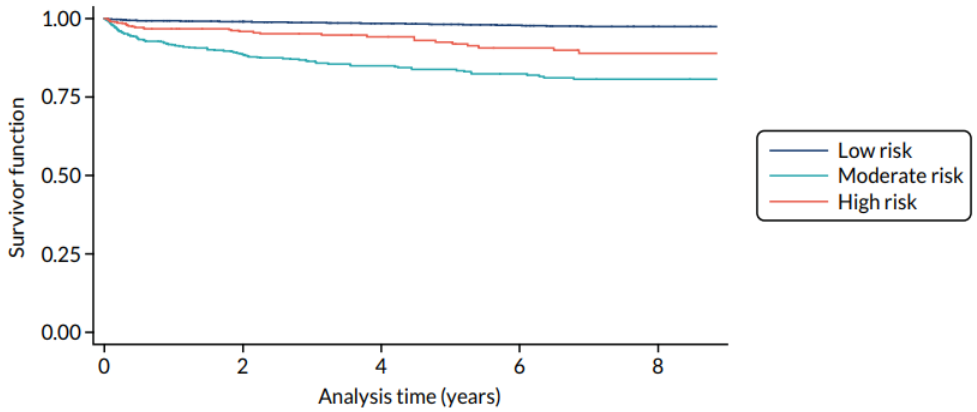


Figure 1. Kaplan-Meier survival estimates. Time to ulceration, stratified by risk status (CPR).

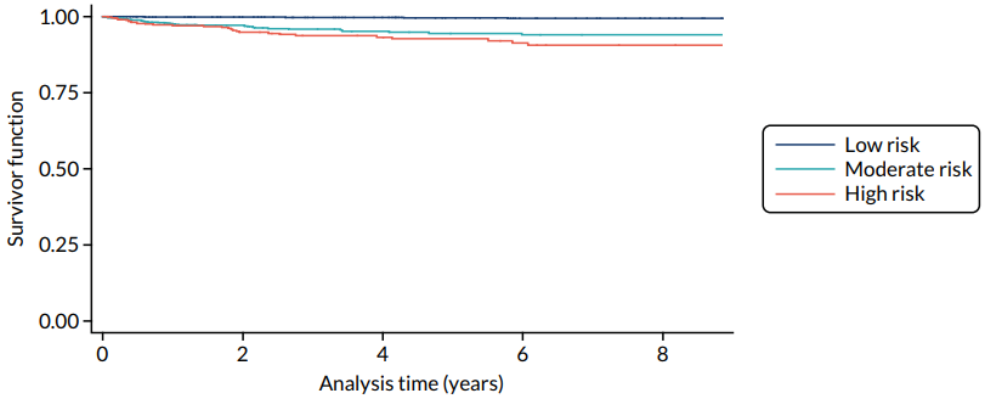


Figure 2. Kaplan-Meier survival estimates. Time to amputation, stratified by risk status (CPR).

Table 13: Person-time and incidence rates of transition from low to moderate risk status (per 1000)

Time period	Cohort person-time	Events	Rate (95% CI)	Quality
0-1 year	9478	172	18.14 (15.62, 21.07)	High
1-2 years	8991	313	34.81 (31.16, 38.88)	High
2-3 years	7805	180	23.06 (19.92, 26.69)	High
3-4 years	6353	114	17.94 (14.93, 21.55)	High
4-5 years	4947	51	10.30 (7.83, 13.56)	High
5-6 years	3655	43	11.76 (8.72, 15.86)	High
6-7 years	2372	11	4.63 (2.56, 8.37)	High
7-8 years	1275	0	0	High
>8 years	359	0	0	High
Total	45,235	884	19.54 (18.29, 20.87)	High

Data taken from Heggie 2020; based on subsample of Crawford 2020 population. N = 10,421

Evidence statements

There is moderate evidence from one retrospective cohort study (Heggie 2020) showing that at 2-year follow-up, the cumulative incidence of ulcer, amputation and death among the low-risk cohort of people with diabetes was 0.4% (95% CI 0.3 to 0.6), 0.1% (95% CI 0.1 to 0.2) and 3.4% (95% CI 3.1 to 3.8), respectively.

2.1.7 Economic evidence

2.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix B). This search retrieved 1304 studies. Based on title and abstract screening, 1303 of the studies could confidently be excluded for this review question. One study was included following the full-text review.

2.1.7.2 Excluded studies

See 0 for excluded studies and reasons for exclusion.

2.1.8 Summary of included economic evidence

The only study identified as partially applicable was by Crawford et al (2020), see This study was still included within this review because the aspects on monitoring which were included are useful to consider when evaluating the cost effectiveness. Crawford et al (2020) has been graded as partially applicable because of these differences in the interventions considered within the analysis compared to the review question.

Table 2 below. This study considers the timing of interventions and treatment strategies by risk status rather than considering monitoring frequency alone which this review question is trying to answer. This study was still included within this review because the aspects on monitoring which were included are useful to consider when evaluating the cost effectiveness. Crawford et al (2020) has been graded as partially applicable because of these differences in the interventions considered within the analysis compared to the review question.

Table 2: Economic evidence profile

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost (£)	Effects (QALYs)	ICER (£/QALY)	
Crawford et al. 2020 based on patients with moderate or severe risk being treated with custom made footwear	Partially applicable:	Minor limitations: 1) Large number of missing data in the electronic health record 2) Based on a Scottish health care system which may have some differences 3) Complete one-way sensitivity analysis was not undertaken	1) The analysis did not explore different monitoring strategy by risk group as based on the clinical prediction rule, the risk group was only used to determine whether preventative treatment was required 2) The analysis did not include the strategy to increase monitoring to every 1-2 months for those patients at high risk, as currently recommended by NICE 3) Custom made footwear was the only preventative measure included in the review as it is currently recommended by NICE 4) Not a complete incremental analysis: all monitoring frequencies compared to standard care	Compared to current practice (defined by natural history of disease and no use of prediction tool): Monitoring every 2 years £133 Monitoring annually £230 Monitoring every 6 months £418 All patients treated £709	Compared to current practice: Monitoring every 2 years 0.013 Monitoring annually 0.014 Monitoring every 6 months 0.014 All patients treated 0.074	Compared to current practice: Monitoring every 2 years Extendedly dominated Monitoring annually Extendedly dominated Monitoring every 6 months Extendedly dominated All patients treated £9,615 Treating all patients was identified as being cost effective at the £20,000 cost per QALY threshold.	Large uncertainty associated with the QALYs for each treatment strategy. Unclear which strategy had the greatest probability of being cost effective at a threshold of £20,000 per QALY.

2.1.9 Economic model

Original health economic modelling was not prioritised for this review question.

2.1.10 Unit costs

The monitoring costs are presented in Table 3. The committee discussed foot screening would take place within the community.

Table 3: Monitoring costs

Resource	Unit costs	Source
Monitoring (Band 4 community based podiatrist – 30 minutes)	£17.50	PSSRU 2020-2021 Assume equivalence in cost as physiotherapists (includes wages and overhead costs) Hourly cost has been adjusted to 30 minutes based on the committee discussion.
Monitoring (Band 5 community based podiatrist – 30 minutes)	£20.50	
Monitoring (Band 6 community based podiatrist – 30 minutes)	£27.00	
Monitoring cost (base year 2017)	£28.60	Crawford et al 2020 inflated

3 The committee's discussion and interpretation of the evidence

The committee discussion of the review on risk assessment tools for diabetic foot problems is combined with the discussion of the review on frequency of diabetic foot reviews.

3.1. The outcomes that matter most

The committee agreed that reducing or preventing ulceration was the critical outcome for both review questions. They argued that if diabetic foot ulcers could be prevented, then subsequent complications and other associated outcomes such as infection, gangrene, amputation and death could also be prevented.

The committee considered the evidence on the prognostic accuracy of the different risk assessment tools, including c-statistics, sensitivity, specificity, and likelihood ratios. It was noted that although sensitivity, specificity and likelihood ratios were not specified as key outcome measures in the original protocol, they were useful outcomes to consider when evaluating the performance of the included assessment tools and it was important to make the best use of the evidence available given the low number of included papers. The committee discussed the relative importance of sensitivity and specificity, and as a group considered whether the priority should be most accurately identifying those at highest risk of developing a diabetic foot ulcer, or identifying and screening out those at lowest risk. They agreed that high sensitivity is key to accurately identifying those at high risk of developing a foot ulcer so that referral to appropriate services, monitoring and preventative treatment can be initiated. However, they also recognised the impact of low specificity in terms of increased monitoring and referral to specialist services for people who are incorrectly assessed as being at high risk, and the demands this may place on services that are already at capacity. Nevertheless, they conceded that this was favourable to lower sensitivity, where the consequences of false negatives could include an increased possibility of ulcer, infection and amputation. As such, the committee agreed that correctly identifying people at high risk to reduce the risk of them having life-altering or life-threatening amputations was more of a priority than screening out people at low risk, despite the potential increase in false positives and associated demands on services. It was noted by lay members of the committee that this was particularly true for high-risk people who have already undergone a lower extremity amputation, where loss of a second leg would be significantly life-altering.

3.2 The quality of the evidence

The committee considered the GRADE quality ratings for all outcomes across the two reviews and noted that for many outcomes it was not possible to assess for imprecision. This was largely because there is no formal guidance on how to assess imprecision for some statistics used in prognostic reviews, so for many outcomes imprecision was rated as not applicable. This can artificially inflate the overall quality rating because the outcome is graded on a reduced number of dimensions, particularly for single study outcomes where inconsistency is also rated as not applicable. For this reason, many of the GRADE quality ratings for outcomes from the Crawford (2020) paper were assessed as high quality, as this was a directly relevant low risk of bias study so no other downgrading was required. Despite this overall high-quality GRADE rating, the committee recognised that this was still only observational evidence and not considered as high quality or robust as evidence generated from randomised controlled trials. This was of less concern for the risk assessment question

where cohort studies were sufficient, but the use of observational evidence for the frequency of foot review question was more of a concern for the committee.

Risk assessment tools

The evidence for the risk assessment review was based on 3 cohort studies. It was not possible to combine results from these 3 studies because they assessed different foot risk assessment tools and reported different statistics across the papers. The committee also noted that several of the assessment tools used different methods to assess diabetic neuropathy, including a 10g monofilament, a tuning fork, and vibration perception threshold using a biothesiometer.

The quality of the included evidence was variable. The Crawford 2020 HTA was a well-conducted study using a large UK-based sample and was assessed as being at low risk of bias. The Chen 2021 study was assessed as moderate risk of bias because it was unclear whether the outcome was determined without prior knowledge of predictor information, and there was uncertainty around some inclusion and exclusion criteria. The Monterio-Soares 2017 paper was assessed as high risk of bias because baseline assessments and outcome diagnoses were conducted by several professionals with varying experience of diabetic foot problems and no reliability assessments were conducted so there may have been variation in the accuracy and reliability of predictor and outcome detection. In addition, outcome assessors were not blind to baseline characteristics and the committee noted that event rates were very low in the community sample which can impact the precision of prognostic accuracy measures. The committee also noted that the paper reported results for PODUS but this was the PODUS prognostic model reported in Crawford 2015 and not the PODUS CPR reported in Crawford 2020, so results for this tool could not be included in this review.

The committee noted the use of a hospital-based population in the Chen 2021 study, many of whom were on insulin, and recognised that hospitalised patients may differ from community-based populations in important ways, including the presence of comorbidities and the potential for immobility. They noted that the risk assessment tools were designed for use in community settings for all people with diabetes, so agreed that the findings from the study of hospitalised patients should be interpreted with this in mind.

Frequency of foot review

The evidence for the review question on frequency of foot screening was based on 1 study. As no RCT evidence was identified, the review was based on descriptive observational evidence only. The initial aim of the review was to compare different foot review frequencies to establish which frequency was most clinically and cost-effective, but in the absence of RCT evidence the review was only able to describe outcomes at a range of follow-up points and draw indirect conclusions about proposed review frequencies. Although overall the study was assessed as being at low risk of bias, the committee noted that the cohort was patients from Fife and they questioned whether the ethnic and social mix of this sample was applicable to the broader UK patient population. In addition, the observational nature of the evidence meant that the committee did not consider this to be high quality robust evidence and it did not directly answer the review question. They agreed that if they were going to make recommendations that would contribute to a significant change to practice by reducing foot screening frequency, this would need to be based on high quality evidence and there was a degree of agreement amongst committee members that the evidence from the HTA was insufficiently robust to justify that change.

3.3 Benefits and harms

Risk assessment tools

The committee discussed the evidence on c-statistics for each of the risk assessment tools. They noted that the c-statistic values ranged between 0.75 and 0.88, representing good to excellent classification accuracy for all tools. The ADA and IWGDF systems both had c-statistics of 0.86 in the Monterio-Soares (2017) paper, and the Crawford (2020) HTA reported a c-statistic of 0.83 for the PODUS, all indicative of excellent classification accuracy. The committee noted that the study comparing c-statistics across all included tools (except for the Chen model and the PODUS) reported no significant differences in c-statistics between any of the risk assessment tools. However, they also noted the wide confidence intervals for the SIGN tool (0.66 to 0.84) and acknowledged that this may have contributed to the absence of a significant difference between the tools. Nevertheless, the committee concluded that overall the tools all performed comparatively well.

As the studies did not report any other outcome measures included in the review protocol, the committee agreed to consider the sensitivity and specificity for each of the risk assessment tools to make best use of the evidence available. They noted that Crawford (2020) did not report on sensitivity or specificity for the PODUS. When considering the highest risk groups only for each measure, the ADA and IWGDF systems showed the same sensitivity (72%) and specificity (87%); the Seattle and UTFRS systems had much lower sensitivity (38% and 31%) but higher specificity (96% and 98%); and the SIGN system had highest sensitivity (91%) but lower specificity (58%). The Chen model showed similar sensitivity and specificity (0.77 and 0.80, respectively). When considering highest risk and moderate risk groups combined, the IWGDF system showed high sensitivity (91%) and acceptable specificity (62%); SIGN had highest sensitivity (94%) but lower specificity (50%); and the ADA, Seattle and UTFRS all performed comparatively well (values around 70-80%). It was concluded that most of the tools performed comparatively well and all were able to predict ulcer occurrence with acceptable accuracy, with the IWGDF and SIGN systems generally showing the best sensitivity and specificity ranges.

Evidence included in the previous guideline similarly found that many of the included risk assessment tools performed comparatively well and therefore the previous guideline committee considered acceptability and current practice when deciding which system to recommend. They considered it important to recommend a specific type of assessment system in order to encourage uniformity of practice across the NHS and agreed that the most widely used system was the SIGN system. In the absence of evidence strongly favouring one system, they agreed by consensus to recommend a risk stratification system based almost entirely on the SIGN risk stratification criteria. The only modification was to include an assessment of renal disease through the addition that those on renal replacement therapy should be treated as high risk.

The committee for the current update also discussed the importance of renal disease and highlighted that this is a known risk factor for diabetic foot and therefore should be included in a risk assessment tool. The committee discussed previous work by the PODUS team that showed kidney disease was not a predictor of diabetic foot ulceration in their model (Crawford 2015), but they reflected on the definition of kidney disease used in these analyses and agreed that it was broader and potentially included patients with less advanced kidney disease than the patients as defined in the existing recommendation (people on renal replacement therapy). They discussed their clinical experiences of foot ulceration in people on dialysis and there was strong consensus that patients on renal replacement therapy are at high risk of developing a foot ulcer. The committee noted that the Chen system was the only one to include renal impairment as a risk factor by assessing diabetic nephropathy. However,

they also noted limitations of the Chen system that precluded them from recommending this tool: primarily that it did not assess for other known risk factors such as history of ulceration or amputation or foot deformity; that it comprised a larger number of items and a more complex calculation than other systems; and that the model validation was based on a hospitalised population so there was uncertainty about its application to community-based populations.

The committee considered the evidence for the PODUS clinical prediction rule and although there were no data on sensitivity or specificity for this tool, they noted that it showed one of the highest c-statistics. They noted that it also had the benefit of being a simpler assessment than other tools as it is based on only 3 main risk factors. They agreed that these assessments could be completed by primary care professionals without specialist knowledge of diabetic foot care, and that the score is simple to interpret, so the tool has the potential to simplify clinical practice by being quick and easy to complete. However, the committee also acknowledged that the SIGN system is not overly complicated and is based on the same 3 main risk factors as the PODUS system but with the addition of assessments for visual impairment, physical impairment, and foot deformity. It was argued that these additional assessments are simple, very brief and would not add any complexity or time taken to complete the risk assessment, relative to the PODUS system. Furthermore, the committee considered foot deformity to be an important clinical indictor for risk of diabetic foot and were reluctant to remove this from the assessment without evidence to demonstrate the benefit of doing so. The PODUS system did not include an assessment of foot deformity in its final model. In an earlier systematic review to identify the most highly prognostic factors for foot ulceration foot deformity was rejected for being inconsistently defined. The committee reflected on their clinical experience, and they disagreed with it being left out of the final PODUS model. For some their experience of working on previous versions of this guideline confirmed this view and stakeholders also emphasised the importance of assessing foot deformity, and agreed that an assessment of foot deformity should still be recommended as part of a foot risk assessment.

Returning to the issue of renal disease, the committee maintained that renal impairment should be included when assessing risk of diabetic foot ulceration, so agreed that this modification to the SIGN system should be retained in the recommendations. The specific modification simply asks if patients are on renal replacement therapy and is therefore not expected to add any significant time or complexity to the foot risk assessment.

More broadly, the committee recognised that the existing modified SIGN system was well established in clinical practice and felt that without good evidence to show that the PODUS system was significantly more clinically and cost-effective, as well as evidence to demonstrate how well it can be implemented as standard practice in the current NHS setting, there was insufficient justification to change the existing recommendation from modified SIGN to PODUS. By recommending PODUS, retraining would be required to complete a new risk stratification system. Several free online training courses aimed at primary care professionals would need changing. Furthermore, primary care IT patient record systems for recording the foot assessments and for referral would also require modifying. The committee did not want to introduce a potentially expensive and time-consuming change in practice without clear evidence of a significant benefit. Especially considering current lower staffing levels and availability for retraining.

Frequency of foot review

The committee considered the evidence showing ulceration rates for the 3 PODUS risk groups (low risk = 3.36%, moderate risk = 16.2%, and high-risk = 38.6%) and the number of people transitioning from low to moderate, and moderate to high risk over the 8-year follow-up period. They agreed that overall, ulceration rates in the low-risk group were very low, and that most people assessed as being at low risk of developing a foot ulcer do not change risk status over time, with the evidence showing that 95.5% of patients assessed as low risk at their first clinical assessment remained in the low-risk group at their final clinical assessment 8 years later. The committee noted that the evidence on the transition from low to moderate risk suggested a higher transition rate in follow-up years 1-2 that then declines over time, but they suggested that this was possibly due to patients being incorrectly screened initially and this then being corrected at their second assessment. This led the committee to consider the quality of foot risk assessments as well as the frequency, and they agreed that some form of governance may be required to monitor the accuracy and reliability of assessments and reduce the risk of people being incorrectly categorised.

The committee agreed that to some extent, the evidence supported a reduction in foot screening frequency from annually to every 2 years, although it was acknowledged that there was no direct evidence to show that screening every 2 years prevented foot ulcers. They agreed that the low ulceration rate in the low-risk group and the low rates of transition from low to moderate risk indicated that a reduction from annual to 2-year foot screening could be feasible. However, many committee members expressed concern about the impact this may have on patient care.

The committee explained how the annual foot check is not just a foot examination and risk assessment, but also provides an opportunity to educate patients about the importance of foot care and how to complete good foot care routines. This often includes demonstrating good foot care practices. It was noted that personal foot care is often something that is done poorly by patients or not at all, with many people feeling uncomfortable dealing with their feet, so there was concern that reducing the opportunity for patients' feet to be examined could be problematic.

The committee highlighted that foot check appointments also provide an opportunity to discuss good diabetes management and physical activity; provide support to modify risk factors; maintain a regular point of contact with services; and educate patients about what to do and where to go should a foot problem develop. The committee explained that for some patients their risk of developing a diabetic foot problem can change very rapidly (e.g., sustaining a foot injury, developing a blister that quickly becomes infected), and this can mean people may move from low risk to high risk very quickly. It was recognised that the frequency of foot screening is unlikely to impact the ability of services to identify those people who progress through the risk groups in this way, but the committee emphasised that it is crucial in these scenarios that patients understand how to respond to urgent foot issues, particularly to prevent them from presenting at A&E in crisis. As such, foot screening appointments were seen as an important opportunity to provide information on signposting to appropriate services and it was agreed that regular, annual repetition of key messages about all aspects of foot care is important.

Some committee members suggested that this education, support and signposting could be offered outside of foot risk assessments and still be offered annually, while reducing the foot screening frequency to every 2 years. The potential of remote appointments for annual information sessions and face to face appointments for a foot check every alternate year was also explored. However, other committee members expressed concern about the feasibility of implementing this in practice. It was noted that the foot check is part of the annual

diabetes review so if patients are attending for that review every year, it seems logical to continue to include a foot examination and risk assessment in that appointment.

The committee considered the potential resource implications of reducing the frequency of foot screening from annually to every 2 years. It was noted that annual screening for all patients is completed in primary care, whereas podiatrists in community foot protection services assess medium- and high-risk patients for intervention and treatment. Therefore, reducing the frequency of screening for low-risk groups in primary care will not free up resource for medium to higher risk patients as they attend a different service. However, the committee agreed that it would free up other primary care resource and they acknowledged the benefits of releasing capacity in general practice.

Having discussed at length the potential benefits and harms of reducing the frequency of diabetic foot screening, and considering the lack of high-quality trial evidence, the committee agreed that on balance it would be appropriate to maintain the current annual foot screening frequency. They agreed that while it is not necessarily the foot check itself that influences patients' risk of developing a foot problem, the opportunity for education, risk modification and signposting can keep people low risk. There was also a degree of agreement that more robust evidence from a clinical trial comparing outcomes across annual and 2-yearly review frequencies would be required before changing recommendations around foot screening review frequency. As a result, the committee made a research recommendation to examine the effectiveness and cost-effectiveness of annual foot assessments compared to 2-yearly foot assessments in reducing diabetic foot problems using a clinical trial. Furthermore, the committee also recognised the importance of real-world evidence in answering this question, so they suggested that using routine real-world healthcare data could also form part of this research recommendation. The triangulation of this data will provide a comprehensive evidence base to determine the future provision of diabetic foot assessments.

3.4 Cost effectiveness and resource use

Risk assessment tools

No relevant published economic evaluations were identified, and no original economic modelling was performed for this research question. Since the clinical evidence suggested that no new risk assessment tool significantly outperformed the SIGN system, the committee's discussion on cost-effectiveness focused mainly on the resource impact associated with different tools. The committee noted that the new PODUS CPR tool has the potential to reduce cost since it involved a shorter and simpler assessment based on only 3 main risk factors. However, according to their clinical experience, the time saving is likely to be negligible since the SIGN system is not over-complicated and has been widely used across the health care system. Switching to a new system can lead to additional costs associated with changing IT systems, extra staff time and trainings to get familiar with the new tool. In addition, the committee were concerned that the PODUS system did not include the presence of deformity or renal disease, both of which are key risk factors for ulceration. Despite its simplicity, there might be more false positives and high-risk cases missed under the PODUS system, which could lead to additional cost impact in the secondary care. Therefore, the committee agreed to keep the current recommendations of the modified SIGN system.

Frequency of foot review

There was only one economic study identified for the review question on monitoring frequency, Crawford et al (2020), which was assessed as partially applicable. It was noted that the standard care defined in the study did not include any form of risk assessment, so is

not in line with the current practice in the NHS. The study is still informative because it shows the increased cost associated with more frequent monitoring and the large uncertainty associated with quality-of-life benefits. The committee described that the current practice for foot monitoring mainly takes place in primary care as part of a patient's annual diabetic check-up. A patient's risk of developing diabetic foot complications is usually assessed using the modified SIGN tool by a health care assistant. People whose risk is classified as medium or high would be referred to podiatry services for preventative treatments and more frequent monitoring of between 3-6 months for people with medium risk and 1-2 months for people identified as having a higher risk.

Although the study found out that the treat all strategy, offering preventive treatments to everyone regardless of their risk status, was the most cost-effective option for patients treated with custom made footwear and offloading or patients treated with digital infrared thermometry, the uncertainty around the results remained high. In addition, the committee agreed that offering preventive treatments to all is not an option to consider in the current health care system and is beyond the scope of this guideline update that focuses on monitoring frequency.

The incremental cost-effectiveness ratio (ICER) for people being monitored every 2 years compared to the standard of care reported by Crawford et al (2020) was below the NICE threshold of £20,000 per QALY gained. Monitoring every 2 years was found to be more cost effective than monitoring annually, but the QALYs remained similar for monitoring every 2 years and monitoring annually. However, given the difference in the definition of standard care and the large uncertainty associated with the QALY estimates for each monitoring frequency, the committee were not confident that the results would be applicable to people with diabetic foot problems in England. Furthermore, the committee felt that the annual review was a key interaction point that allowed the importance of foot care to be reminded and to discuss and review other aspects of diabetes care. There were also concerns that reducing the frequency of foot monitoring would incorrectly signal that foot care isn't a priority and lead to more people with foot problems developing into higher risk status at a later point, which would have a considerable impact on both resources and on patients' wellbeing. The committee also raised concerns that the proportion of patients attending their annual foot check-up had decreased considerably during the coronavirus pandemic. Any decrease in monitoring frequency would lead to a further decrease in the proportion of people attending foot reviews, which could add additional burden on the over-stretched secondary care system since more people at medium and high risk might develop active foot problems and need to seek for hospital treatments at a later point. Therefore, the committee agreed that we did not have sufficient economic evidence to recommend a longer monitoring interval of every 2 years.

3.5 Other factors the committee took into account

The committee agreed that education about the importance of foot care and what to do if a problem develops was one of the most important aspects of the annual diabetic foot assessment. They noted that the existing guideline contained a section on 'patient information about the risk of developing a diabetic foot problem,' with recommendations covering all of the information discussed by the committee (1.3.13 and 1.3.14). To avoid duplication but give the section more prominence, the committee agreed to add a link to this section in recommendation 1.3.7.

The committee considered issues relating to public perception and the views of patients who may be concerned about the safety and implications of a reduction from annual to 2-yearly foot screening. They reflected on the widespread perception that many NHS services are

looking to make cuts and save money, and expressed concern that a decision to reduce the frequency of foot screening based on low quality observational evidence may be perceived as driven by cost-savings rather than evidence or patient care. They anticipated that many patients would be reassured that the frequency of their foot review would not change, and that 'normal service' is being re-instated post-COVID. This view was supported by lay members of the committee with patient experience of diabetic foot problems. The committee also noted that many health care professionals are experiencing 'change fatigue' and will likely be reassured that diabetic foot risk assessment procedures will remain the same and not require new training, policies or paperwork.

The committee considered potential equality issues and highlighted that people with diabetes that are male, from the most deprived areas, aged over 65 or of white ethnicity had greater risk of both major and minor limb amputation. This disparity was also reported in the National Diabetes Foot Care Report published by the Office for Health Improvement and Disparities (December 2021). The committee discussed the possible need to include known demographic-based risk factors of male sex, older age and white ethnicity to the risk assessment systems, but agreed that diabetic foot risk assessment tools should focus on clinical indictors only. The committee agreed that recommendations targeting specific higher risk population groups were not needed as there were local practices in place to target these groups to ensure they attend their annual foot assessments.

At draft guideline consultation, an issue was raised regarding groups who need additional consideration to encourage foot screening. People with type 2 diabetes who have put the condition into remission should be included, especially those with a history of micro and macrovascular complications. Despite their diabetes being in remission, these individuals may still experience diabetes related complications. Whilst there is no clear data on their experience of foot care currently, concern was raised that this growing population may be at risk of being overlooked for annual screening. The committee agreed with this view and noted that within primary care patients coded as diabetes in remission will automatically be invited for annual diabetes retinal screening, will need continued review for micro and macro vascular complications, i.e., annual diabetes review checks (which will include foot assessments), and for the development of hyperglycaemia. Furthermore, the committee suggested that people with type 1 diabetes not on insulin (such as those with a pancreas transplant) should also be included for additional consideration.

In response to stakeholder feedback, the committee considered the use of certain terminology in some recommendations. First, they noted that the use of 'red foot' in recommendation 1.3.6 for describing signs of an active diabetic foot problem may not adequately consider diversity in skin tones, particularly on dark skin where 'red' may not be evident. The committee therefore agreed to change this to 'change in colour.' The committee also reflected on the language of 'diabetic foot' and acknowledged the views of some stakeholders that there is the potential for this to be discriminatory or not inclusive for people with diabetes. They considered more inclusive, person-centred terms, such as 'foot problem associated with diabetes,' but noted the potential complexity of rewording almost every recommendation in the guideline. They also reflected on the terminology used in other guidelines, including diabetic retinopathy, diabetic neuropathy and diabetic ketoacidosis, and concluded that 'diabetic foot' is an accepted medical term used to name a medical problem. The committee therefore agreed to retain this terminology throughout the guideline, but provided a definition of 'diabetic foot problems' in the 'terms used in this guideline' section which included reference to the more person-centred language of 'people with diabetes who have a foot problem.'

Finally, the committee discussed the role of digital and emerging technologies for assessing the risk of developing a diabetic foot problem and the potential role they can play in both assessment and prevention. The committee therefore made a research recommendation to determine whether access to new technologies can improve diabetic foot assessments, expand the number of health care professionals who can undertake foot screening, improve screening accuracy, and prevent the development of foot ulcers.

3.6 Recommendations supported by this evidence review

No new recommendations were made from this evidence review.

3.7 References – included studies

3.7.1 Clinical

Review 1.1 – Risk assessment tools

Chappell, FM, Crawford, F, Horne, M et al. (2021) Development and validation of a clinical prediction rule for development of diabetic foot ulceration: an analysis of data from five cohort studies. BMJ open diabetes research & care 9(1)

Chen, Dong, Wang, Meijun, Shang, Xin et al. (2021) Development and validation of an incidence risk prediction model for early foot ulcer in diabetes based on a high evidence systematic review and meta-analysis. Diabetes research and clinical practice 180: 109040

Crawford, Fay, Chappell, Francesca M, Lewsey, James et al. (2020) Risk assessments and structured care interventions for prevention of foot ulceration in diabetes: development and validation of a prognostic model. Health technology assessment (Winchester, England) 24(62): 1-198

Monteiro-Soares, M, Ribas, R, Pereira da Silva, C et al. (2017) Diabetic foot ulcer development risk classifications' validation: A multicentre prospective cohort study. Diabetes research and clinical practice 127: 105-114

Review 2.1 – Frequency of foot review

Crawford, Fay, Chappell, Francesca M, Lewsey, James et al. (2020) Risk assessments and structured care interventions for prevention of foot ulceration in diabetes: development and validation of a prognostic model. Health technology assessment (Winchester, England) 24(62): 1-198

Heggie, R, Chappell, F, Crawford, F et al. (2020) Complication rate among people with diabetes at low risk of foot ulceration in Fife, UK: an analysis of routinely collected data. Diabetic medicine : a journal of the British Diabetic Association 37(12): 2116-2123

3.7.2 Economic Review 2.1 – Frequency of foot review

Crawford, Fay, Chappell, Francesca M, Lewsey, James et al. (2020) Risk assessments and structured care interventions for prevention of foot ulceration in diabetes: development and validation of a prognostic model. Health technology assessment (Winchester, England) 24(62): 1-198

3.7.3 Other

Personal Social Services Research Unit. Unit Costs of Health and Social Care 2021. Published online 2021. https://www.pssru.ac.uk/project-pages/unit-costs/

Appendices

Appendix A – Review protocols

A.1 Review protocol for Diabetic Foot Problems – Prevention and Management: Risk assessment tools for predicting the development of diabetic foot problems

ID	Field	Content
0.	PROSPERO registration number	CRD42022339464
1.	Review title	Risk assessment tools for predicting the development of diabetic foot problems
2.	Review question	In people with diabetes which risk assessment models/tools better predict the development of diabetic foot problems?
3.	Objective	To determine which risk assessment models/tools better predicts the development of diabetic foot problems, including: • foot ulcers (including severity) • soft tissue infections • osteomyelitis • gangrene • amputation

4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Health Technology Assessment Database (HTA) Searches will be restricted by: • 21st August 2014 onwards • English language • Human studies Other searches: • Inclusion lists of systematic reviews The full search strategies will be published in the final review.
5.	Condition or domain being studied	Diabetic foot problems: prevention and management

6.	Population	Inclusion: People with type 1 or type 2 diabetes.
7.	Intervention/Exposure/Test	Inclusion: Risk assessment models/tools for predicting the development of diabetic foot problems. Exclusion: Tools for the classification of foot ulcer severity or diagnosis of foot infection (e.g. SINBAD or WIfi classification system).
8.	Comparator/Reference standard/Confounding factors	Other risk assessment tools (including existing NICE recommendations on the assessment of diabetic foot problems)
9.	Types of study to be included	• Prospective cohort studies • Model validation studies • Model impact studies • Systematic reviews of these studies
10.	Other exclusion criteria	• All other study types. • Model development studies that do not report model validation data.
11.	Context	New evidence from a health technology assessment (HTA) on 'risk assessments and structured care interventions for prevention of foot ulceration in diabetes: development and validation of a prognostic model' (Crawford et al. 2020), indicates that 1) there is an alternative risk assessment tool for foot ulceration that may be simpler than the currently recommended risk assessment

		2) risk assessments may be undertaken at 2-yearly intervals in low-risk groups instead of annually.
12.	Primary outcomes (critical outcomes)	Clinical endpoints: • Progression to - foot ulcers (including severity) - soft tissue infections - osteomyelitis - gangrene resulting from diabetes - amputation (major and minor) - Charcot arthropathy - Critical limb ischemia / chronic limb threatening ischemia - All-cause mortality For each outcome, metric measures will be reported where available, for example: • Odds ratios//hazard ratios • Model fit statistics (for example R^2, Brier score) • Discrimination (for example C statistic, area under ROC curve). • Calibration (for example calibration slope)

		We will report the time horizon for prediction as reported in the studies
13.	Secondary outcomes (important outcomes)	
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.2).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For prognostic reviews this is the PROBAST checklist.
16.	Strategy for data synthesis	Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect. All key outcomes from evidence will be presented in GRADE profiles and evidence statements will be used when outcomes cannot be GRADED.

17.	Analysis of sub-groups	Age Sex Ethnicity Duration of diabetes Type 1 or type 2 diabetes Presence of renal disease
18.	Type and method of review	☐ Intervention ☐ Diagnostic ☒ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)

19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins. A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]		
22.	Anticipated completion date	August 2023		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches		

		Piloting of the study selection process		
		Formal screening of search results against eligibility criteria		
		Data extraction		
		Risk of bias (quality) assessment		

		Data analysis		
24.	Named contact	**5a. Named contact** Guideline Development Team **5b. Named contact e-mail** Diabetesupdate@nice.org.uk **5c. Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and Guideline Development Team		
25.	Review team members	From the Guideline Development Team: • Caroline Mulvihill • Hannah Stockton • Miaoqing Yang • Kirsty Hounsell • Dave Nicholls		
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team, Centre for Guidelines which receives funding from NICE.		

27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Project information | Diabetic Foot Problems: Prevention and management (update) | Guidance | NICE
29.	Other registration details	[Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.]

30.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Diabetic foot; risk prediction tool; risk stratification tool;
33.	Details of existing review of same topic by same authors	
34.	Current review status	☒ Ongoing ☐ Completed but not published

		☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	
36.	Details of final publication	www.nice.org.uk

A2. Review protocol for Diabetic Foot Problems – Prevention and Management: Frequency of review for people with diabetes who are at low risk, moderate risk, or high risk of developing a diabetic foot problem or needing an amputation.

ID	Field	Content
0.	PROSPERO registration number	CRD42022339480
1.	Review title	How often should people with diabetes who are at low risk, moderate risk, or high risk of developing a diabetic foot problem or needing an amputation be reviewed?
2.	Review question	How often should people with diabetes who are at low risk, moderate risk, or high risk of developing a diabetic foot problem or needing an amputation be reviewed?

3.	Objective	To determine the appropriate review frequency for people with diabetes according to the risk of developing foot problems.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase (Ovid) • MEDLINE (Ovid) • Health Technology Assessment Database (HTA) Searches will be restricted by: • 21st August 2014 - current • English language • Human studies Other searches: • Inclusion lists of systematic reviews The full search strategies will be published in the final review.
5.	Condition or domain being studied	Diabetic foot problems: prevention and management
6.	Population	Inclusion: People with type 1 or type 2 diabetes.

7.	Intervention/Exposure/Test	Review schedules of varying frequency for the risk categories.
8.	Comparator/Reference standard/Confounding factors	Standard care based on risk category.
9.	Types of study to be included	Systematic reviews Randomised controlled trials If insufficient evidence is available progress to: - Non-randomised controlled trials - Comparative observational studies
10.	Other exclusion criteria	Exclusion: Other study types
11.	Context	New evidence from a health technology assessment (HTA) on 'risk assessments and structured care interventions for prevention of foot ulceration in diabetes: development and validation of a prognostic model' (Crawford et al. 2020), indicates that 1) there is an alternative risk assessment tool for foot ulceration that may be simpler than the currently recommended risk assessment 2) risk assessments may be undertaken at 2-yearly intervals in low-risk groups instead of annually.
12.	Primary outcomes (critical outcomes)	1. Foot ulcer incidence (including severity) 2. Soft tissue infections

		3. Osteomyelitis 4. Gangrene incidence resulting from diabetes 5. Amputation incidence (major and minor) 6. Charcot arthropathy 7. Critical limb ischemia / chronic limb threatening ischemia 8. All-cause mortality 9. Rates of A&E presentation / hospital admission for foot problems resulting from diabetes (Non-scheduled clinical encounters relating to diabetic foot problems)
13.	Secondary outcomes (important outcomes)	1. Resource use and costs 2. Quality of life 3. Cardiovascular outcomes (if data allows)
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.2). Study investigators may be contacted for missing data where time and resources allow.

15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Randomised control trials (individuals or cluster) will be assessed using the Cochrane risk of bias tool 2.0. Assessment of observational studies will be dependent on study design. Cohort studies will be assessed using the Cochrane ROBINS-I tool.
16.	Strategy for data synthesis	Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect. All key outcomes from evidence will be presented in GRADE profiles and evidence statements will be used for outcomes that cannot be GRADED.
17.	Analysis of sub-groups	Age Sex Ethnicity Duration of diabetes Type 1 or type 2 diabetes Presence of renal disease

18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins. A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]

<table>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="3">[Give the date by which the guideline is expected to be published. This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.]</td></tr>
<tr><td rowspan="5">23.</td><td rowspan="5">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td></td><td></td></tr>
<tr><td>Piloting of the study selection process</td><td></td><td></td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td></td><td></td></tr>
<tr><td>Data extraction</td><td></td><td></td></tr>
</table>

		Risk of bias (quality) assessment		
		Data analysis		
24.	Named contact	**5a. Named contact** Guideline Development Team **5b. Named contact e-mail** Diabetesupdate@nice.org.uk **5c. Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and Guideline Development Team		
25.	Review team members	From the Guideline Development Team: • Caroline Mulvihill • Hannah Stockton • Miaoqing Yang • Kirsty Hounsell • Dave Nicholls		

26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team, Centre for Guidelines which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Project information | Diabetic Foot Problems: Prevention and management (update) | Guidance | NICE
29.	Other registration details	[Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.]
30.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]

31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Diabetic foot; risk assessment; review frequency
33.	Details of existing review of same topic by same authors	[Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible. NOTE: most NICE reviews will not constitute an update in PROSPERO language. To be an update it needs to be the same review question/search/methodology. If anything has changed it is a new review]
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued

35..	Additional information	
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Table 1: search strategy

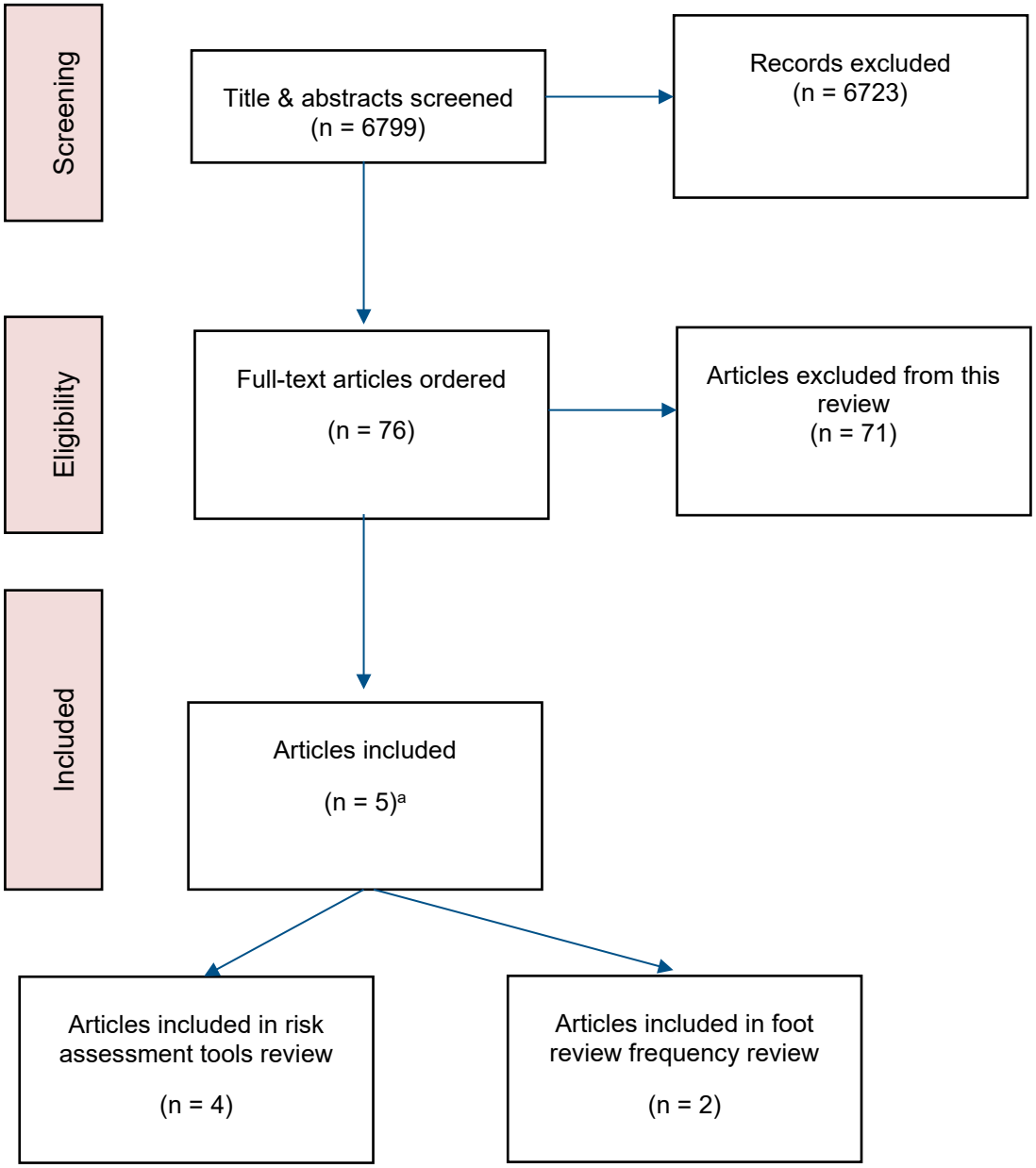
Medline Strategy, searched 16 May 2022 **Database: Ovid MEDLINE(R) <1946 to May 13, 2022>** **Search Strategy:**
1 exp Diabetes Mellitus/ (479211)
2 Diabet*.tw. (627987)
3 or/1-2 (692378)
4 exp Foot Diseases/ (22380)
5 Ulcer/ (14809)
6 Gangrene/ (8320)
7 Osteomyelitis/ (21617)
8 (ulcer* or gangrene* or osteomyelit*).tw. (227567)
9 soft tissue infections/ or wound infection/ (15629)
10 ((Foot* or feet* or toe* or tissue* or wound*) adj4 (infect* or disease*)).tw. (108540)
11 Arthropathy, Neurogenic/ (1796)
12 Charcot-Marie-Tooth Disease/ (4288)
13 Charcot*.tw. (7150)
14 Amputation/ (22963)
15 amputat*.tw. (40265)
16 Chronic Limb-Threatening Ischemia/ (169)
17 ((Foot* or feet* or toe* or limb*) adj4 (ischem* or ischaem*)).tw. (13419)
18 or/4-17 (422710)
19 3 and 18 (26516)
20 Diabetic Foot/ (10453)
21 (Diabe* adj4 (foot* or feet* or toe*)).tw. (10058)
22 or/19-21 (29134)
23 exp Risk Assessment/ (303570)
24 (risk* adj2 (stratif* or assess* or analy* or benefit* or classifi* or model* or tool* or adjust* or evaluat* or categor* or system* or score* or level* or check* or group* or grade*)).tw. (356537)
25 ((proactiv* or pro-activ* or pro activ*) adj4 care).tw. (992)
26 "Predictive Value of Tests"/ (220922)
27 (predict* adj2 value*).tw. (132171)
28 or/23-27 (849586)
29 exp Patient Care Planning/ (66905)
30 "Appointments and Schedules"/ (9660)
31 "continuity of patient care"/ (20361)
32 time factors/ (1227293)
33 ((review* or appointment* or care* or manag* or (follow adj1 up*) or follow-up* or monitor*) adj4 (schedule* or frequen* or program* or itinerar* or plan* or schedule* or practice* or assess* or outcome* or year* or annual* or interval*)).tw. (758677)
34 ((early or earliest) adj1 (awareness or detect* or diagnos*)).tw. (152092)
35 Monitoring, Physiologic/ (57908)

Medline Strategy, searched 16 May 2022 Database: Ovid MEDLINE(R) <1946 to May 13, 2022> Search Strategy:
36 ((increas* or expan* or additional* or raise* or decreas* or reduc* or lower* or fewer* or routine* or standard* or frequen* or regular* or rate or rates or optim* or repeat*) adj4 (monitor* or assess* or surveil* or observ* or exam* or follow-up* or followup* or check-up* or checkup*)).tw. (724592) 37 monitor.ti. (11199) 38 or/29-37 (2784571) 39 28 or 38 (3436161) 40 22 and 39 (7465)

Table 2: Study design filters

The study filters and limiting search strategies used as part of the literature searches are presented below.
RCT 1 randomized controlled trial.pt. 2 randomi?ed.mp. 3 placebo.mp. 4 or/1-3
Systematic Review 1 MEDLINE or pubmed).tw. 2 systematic review.tw. 3 systematic review.pt. 4 meta-analysis.pt. 5 intervention$.ti. 6 or/1-5
Observational Studies 1 Observational Studies as Topic/ 2 Observational Study/ 3 Epidemiologic Studies/ 4 exp Case-Control Studies/ 5 exp Cohort Studies/ 6 Cross-Sectional Studies/ 7 Controlled Before-After Studies/ 8 Historically Controlled Study/ 9 Interrupted Time Series Analysis/ 10 Comparative Study.pt. 11 case control$.tw. 12 case series.tw. 13 (cohort adj (study or studies)).tw. 14 cohort analy$.tw. 15 (follow up adj (study or studies)).tw. 16 (observational adj (study or studies)).tw. 17 longitudinal.tw. 18 prospective.tw. 19 retrospective.tw. 20 cross sectional.tw. 21 or/51-70

Appendix C – Evidence study selection



[a] Note that one study was included in both reviews so total articles included = 5

Appendix D – Evidence Tables

D1. Prognostic evidence

Chen, 2021

Bibliographic Reference	Chen, Dong; Wang, Meijun; Shang, Xin; Liu, Xixi; Liu, Xinbang; Ge, Tiantian; Ren, Qiuyue; Ren, Xiaoxia; Song, Xin; Xu, Hongmei; Sun, Mingyan; Zhou, Hongmei; Chang, Bai; Development and validation of an incidence risk prediction model for early foot ulcer in diabetes based on a high evidence systematic review and meta-analysis.; Diabetes research and clinical practice; 2021; vol. 180; 109040

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Tianjin, China Study setting Tianjin Medical University Chu Hsien-I Memorial Hospital Study dates 01/01/2016 to 01/01/2021 Sources of funding This work was supported by the National Natural Science Foundation of China (81973614)

Inclusion criteria	Criteria 1 Patients with type 2 diabetes hospitalised more than twice between 01/01/2016 and 01/01/2021. Patients did not develop an active foot ulcer during their first hospitalisation and developed diabetic foot ulcer in their last hospitalisation. Criteria 2 Aged between 39 and 75 years
Exclusion criteria	Criteria 1 Excluded patients who were hospitalised for reasons such as acute foot injury, malignancy, myocardial infarction, end stage renal disease, or other serious infectious diseases. Criteria 2 Type 1 diabetes Criteria 3 Patients initially hospitalised for diabetic foot ulcer Criteria 4 Patients who were followed up for <1 year Criteria 5 Patients with incomplete baseline information
Number of participants and recruitment methods	Final validation cohort n = 465

Length of follow-up	Median follow-up period 27 months
Outcome(s) of interest	Occurrence of diabetic foot ulcer, defined as full-thickness skin ruptures that occur at least at Wagner stage 1 or above, occurring at the distal end of the ankle. For model validation, area under the curve (AUC) through receiver operating characteristic (ROC) curves was calculated. Participants were also divided into 4 risk groups based on the optimal cut-off point and Kaplan-Meier curves were used to compare the cumulative risk in the different groups.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	**Sex** Female (risk score = 0) Male (risk score = 6) **BMI** < 24.00 (risk score = 0) 24.00-27.99 (risk score = 4) ≥28.00 (risk score = 8) **HbA1c (% [mmol/ mol])** < 7.0 [<53] (risk score = 0 7.0-7.9 [53-63] (risk score = 2) 8.0-8.9 [64-74] (risk score = 4) ≥9.0 [≥75] (risk score = 6)

	Smoker No (risk score = 0) Yes (risk score = 6) **Diabetic nephropathy (defined as eGFR < 60 mL/min/1.73m2 and/or severe albuminuria ACR > 300 mg/mmol or > 3000 mg/g caused by DM for >3 months)** No (risk score = 0) Yes (risk score = 11) **Diabetic retinopathy (confirmed by opthalmoscopy)** No (risk score = 0) Yes (risk score = 11) **Diabetic peripheral neuropathy (confirmed using a combination of signs, symptoms and nerve conduction function)** No (risk score = 0) Yes (risk score = 11) **Intermittent claudication (indicative of peripheral arterial disease)** No (risk score = 0) Yes (risk score = 13)

	Foot care (includes regular foot washing, daily foot self-examination, not barefoot walking, not wearing slippers or loose fitting socks, and examination by a foot specialist at least once a year) No (risk score = 9) Yes (risk score = 0) **Scoring system:** <28.5 = low risk 29-46.5 = low-intermediate risk 47-57.5 = high-intermediate risk 58-80 = high risk
Additional comments	Study limitations: 1. Patients in the model derivation cohort were from USA, Brazil, Canada, UK, Denmark, Norway, Italy, China, South Korea, Iran, Japan, Australia and Ethiopia, while patients in the model validation cohort were from China only. Multicentre external validation is still necessary. 2. In the validation cohort, the number of participants taking insulin was large (72.9%), which may cause bias 3. The model was based on results of a meta-analysis of risk factors for DFU but some other known clinical indicators were not identified as risk factors in the studies included in the meta-analysis (e.g. previous ulceration, amputation and the presence of foot deformity). 4. Study included people with type 2 diabetes only.

Population characteristics

Study-level characteristics

Characteristic	Study (N = 465)
% Female Sample size	n = 177; % = 38.1
Mean age (SD) Mean (SD)	56.9 (9.8)
Developed diabetic foot ulcer during follow-up period No of events	n = 65; % = 13.98
HBA1C (70 mmol/mol) Median (IQR)	8.6 (7.45 to 9.7)
Diabetes duration (years) Median (IQR)	12 (8 to 17)
BMI Mean (SD)	26.8 (3.8)
Patients who smoked Sample size	n = 193; % = 41.5
Patients receiving oral hypoglycemic therapy Sample size	n = 452; % = 97.2

Characteristic	Study (N = 465)
Patients treated with insulin Sample size	n = 339; % = 72.9

Critical appraisal - PROBAST tool

Overall Risk of bias and Applicability	Risk of bias	Moderate
Overall Risk of bias and Applicability	Concerns for applicability	Low

Crawford, 2020

Bibliographic Reference Crawford, Fay; Chappell, Francesca M; Lewsey, James; Riley, Richard; Hawkins, Neil; Nicolson, Donald; Heggie, Robert; Smith, Marie; Horne, Margaret; Amanna, Aparna; Martin, Angela; Gupta, Saket; Gray, Karen; Weller, David; Brittenden, Julie; Leese, Graham; Risk assessments and structured care interventions for prevention of foot ulceration in diabetes: development and validation of a prognostic model.; Health technology assessment (Winchester, England); 2020; vol. 24 (no. 62); 1-198

Study Characteristics

Study design	Prospective cohort study
Study details	Study location UK

	Study setting Community setting - community and hospital foot clinics Study dates Recruitment ranged from 28th January 2001 to 8th December 2006; final follow-up was 2007 Sources of funding This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme
Inclusion criteria	Criteria 1 Patients had diabetes mellitus Criteria 2 Predictors had been assessed at recruitment and foot ulcer status assessed at follow-up Criteria 3 Patients had to be aged ≥18 years and ulcer free at the time of recruitment
Number of participants and recruitment methods	Development cohort: Data from 4 studies were used to form the development cohort: Abbott (2002) n=6603, recruited 6603 patients in Manchester from several different settings, including general medical practices, diabetes specialist centres, hospital outpatient departments and podiatry clinics. The second UK-based cohort (Crawford 2011) was conducted in Tayside in Scotland which included 1193 people recruited from community podiatry clinics. The third study was Pham (2000) and included 248 people with diabetes recruited from one of three large diabetic foot centres in the USA. The fourth study was Monteiro-Soares (2010) and recruited 360 patients from a public tertiary hospital in Portugal.

	(Information taken from Crawford 2015). <u>Validation cohort</u> Data from Leese et al. (2011) was used to validate the model, using data from 3412 patients. This validation dataset was from an electronic register, which had taken data from General Practice records and Information Services Division NHS Scotland (information taken from Chappell 2021).
Length of follow-up	2 years
Loss to follow up	Development cohort: "The number of patients in the development datasets was 8404, and the number who contributed to the analyses was 8255 (98%)." (information taken from Chappell 2021) Validation cohort: Of the 3412 participants recruited, there were 3324 participants with suitable data (no specific information on loss to follow-up)
Outcome(s) of interest	Presence or absence of foot ulceration within 2 years
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	PODUS CPR predictors: - Insensitivity to a 10-g monofilament at any site on either foot (score 1 if insensitive) - Absent pedal pulses (either dorsalis pedis or posterior tibial) on either foot (score 1 if any pedal pulse is absent) - History of ulceration or amputation (score 2 if history of previous ulcer or amputation) Scores range from 0 to 4.

Covariates adjusted for in the multivariable regression modelling	
Additional comments	Although the study recorded patients' test dates, in the case of occurrence only the year was recorded. Therefore, the authors recorded an ulcer having occurred within 2 years if one was recorded within 2 years of the year that the patient was first seen. This is not a precise way of coding ulcer outcome by 2 years, but allowed the authors to use the data set for externally validating the model.

Population characteristics

Study-level characteristics – Development cohort

Characteristic	**Study (N = 8404)**
% Female Sample size	n = 3989; % = 47.5
Mean age (SD) Range	18 to 95
Mean age (SD) Mean (SD)	62.7 (13.1)
Duration of diabetes (years) Mean (SD)	8.8 (8.6)

Characteristic	Study (N = 8404)
No ulcer No of events	n = 7960; % = 94.7
Ulcer No of events	n = 435; % = 5.2

Study-level characteristics – Validation cohort

Characteristic	Study (N = 3412)
% Female Sample size	n = 1481; % = 43.4
Mean age (SD) Range	19 to 101
Mean age (SD) Mean (SD)	65.1 (13.1)
Duration of diabetes (years) Mean (SD)	6.8 (7.8)
No ulcer No of events	n = 3279; % = 96.1

Characteristic	Study (N = 3412)
Ulcer No of events	n = 133; % = 3.9

Critical appraisal - PROBAST tool

Overall Risk of bias and Applicability	Risk of bias	Low
Overall Risk of bias and Applicability	Concerns for applicability	Low

Monteiro-Soares, 2017

Bibliographic Reference	Monteiro-Soares, M; Ribas, R; Pereira da Silva, C; Bral, T; Mota, A; Pinheiro Torres, S; Morgado, A; Couceiro, R; Ribeiro, R; Dias, V; Moreira, M; Mourao, P; Oliveira, M J; Madureira, M; Paixao-Dias, V; Dinis-Ribeiro, M; Diabetic foot ulcer development risk classifications' validation: A multicentre prospective cohort study.; Diabetes research and clinical practice; 2017; vol. 127; 105-114

Study Characteristics

Study design	Prospective cohort study
Study details	Study location Portugal Study setting

	Diabetic foot clinics at a tertiary hospital and two primary care institutions Study dates December 2010 to December 2012 for the tertiary hospital; July 2013 to September 2014 for one primary care institution; and March to September 2014 for the other primary care institution Sources of funding Matilde Monteiro-Soares was funded by ‘‘Fundac¸a˜o para a Cieˆncia e Tecnologia (FCT)”, Portugal; Grant number: SFRH/ BD/86201/2012.
Inclusion criteria	Criteria 1 People with diabetes and without active DFU, who underwent diabetic foot screening in an included setting
Exclusion criteria	Criteria 1 People unable to walk and / or unable to respond adequately to foot examination tests
Number of participants and recruitment methods	N = 446 (223 from each setting: hospital and primary care) Patients that underwent diabetic foot screening in one of the 3 included settings were consecutively included.
Length of follow-up	Median follow-up = 12 months (range 1-12 months). Participants were followed-up for one year or until outcome occurred (DFU) or death. Participants were re-assessed in variable intervals (between 1 and 6 months) according to the IWGDF recommendations and the health professionals' clinical judgement.
Loss to follow up	N = 61 (14%) were lost to follow-up. A participant was considered as lost to follow up when he or she missed the scheduled appointment(s) and did not return before the 1 year follow up. When this occurred, the subjects’ clinical electronic file and the National Health Platform was consulted to identify if a DFU or death occurred in another institution

Outcome(s) of interest	Diabetic foot ulcer (DFU); defined as a full-thickness skin defect distal to the malleoli.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	The DFU risk classification systems tested in this study were: - The American Diabetes Association (ADA) classification - The International Working Group on the Diabetic Foot (IWGDF) classification - The Scottish Intercollegiate Grouping Network (SIGN) classification - The Seattle risk score (both in its original and refined version) - The University of Texas Foot Risk System (UTFRS) At baseline, all variables included in the classifications and other relevant clinical characterisation variables were collected through clinical interview, foot examination, or clinical file consult. Clinical variables were collected by several professionals, namely GPs and nurses in the primary care setting and podiatrists in the hospital setting. Relevant variables included: history of previous DFU, visual and physical impairment, recent HbA1c value, presence of foot deformity, hyperkeratosis, foot self-care habits, previous LEA, diabetic peripheral neuropathy (diagnosed through SWM and/or tuning fork), peripheral arterial disease (diagnosed through pedal pulses).
Additional comments	Study limitations: 1.) The number of DFU in the primary care setting was very low (n=3; 1%), which greatly affects the diagnostic accuracy measures precision and diminished the PPV values. Similarly, the study did not reach the 100 events that are recommended for prediction model validation. 2.) The experience of the people collecting the data was variable and no reliability assessments were conducted for detection of the predictive variables, the classifications, or outcome recognition. However, the authors argue that by including health professionals with different levels of experience, they better portray the reality of clinical care in this topic.

	3.) Researchers were not blind to baseline characteristics when assessing DFU occurrence. 4.) The authors sought to simplify the diagnosis of DPN and PAD by using only the tuning fork and foot pulses, respectively. This may have underestimated the classifications' accuracy measures (although the authors argue this nevertheless simplifies the classifications' application and therefore use in clinical practice). 5.) 99% of the sample had type 2 diabetes which may impact the generalisability of the results.

Study arms

All (N = 446)

Hospital setting (N = 223)

Community setting (N = 223)

Population characteristics

Arm-level characteristics

Characteristic	All (N = 446)	Hospital setting (N = 223)	Community setting (N = 223)
% Female Sample size	n = 213; % = 48	n = 95; % = 43	n = 118; % = 53
Mean age (SD)	65 (11)	65 (10)	65 (10)

Characteristic	All (N = 446)	Hospital setting (N = 223)	Community setting (N = 223)
Mean (SD)			
Body mass index Mean (SD)	29 (5)	29 (6)	29 (5)
Lives alone Sample size	n = 39; % = 9	n = 12; % = 5	n = 27; % = 12
Type 2 diabetes Sample size	n = 443; % = 99	n = 223; % = 100	n = 220
Diabetes duration (in years) Mean (SD)	13 (10)	16 (11)	9 (8)
Insulin use Sample size	n = 136; % = 31	n = 106; % = 48	n = 30; % = 14
Reported retinopathy Sample size	n = 111; % = 25	n = 90; % = 40	n = 21; % = 10
Reported nephropathy Sample size	n = 58; % = 13	n = 45; % = 20	n = 12; % = 6
Developed a DFU during follow-up period No of events	n = 32; % = 7.2	n = 29; % = 13	n = 3; % = 1.3

Critical appraisal - PROBAST tool

Overall Risk of bias and Applicability	Risk of bias	High *(Use of a large number of HCPs with a range of experience of diabetic foot for predictor and outcome assessments could introduce bias. Outcome assessors were not blind to baseline variables. Low number of patients developed the outcome.)*
Overall Risk of bias and Applicability	Concerns for applicability	Low *(99% of the sample had type 2 diabetes.)*

D2. Observational evidence

Crawford, 2020

Bibliographic Reference	Crawford, Fay; Chappell, Francesca M; Lewsey, James; Riley, Richard; Hawkins, Neil; Nicolson, Donald; Heggie, Robert; Smith, Marie; Horne, Margaret; Amanna, Aparna; Martin, Angela; Gupta, Saket; Gray, Karen; Weller, David; Brittenden, Julie; Leese, Graham; Risk assessments and structured care interventions for prevention of foot ulceration in diabetes: development and validation of a prognostic model.; Health technology assessment (Winchester, England); 2020; vol. 24 (no. 62); 1-198

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location Fife, Scotland Study setting Data collected from records relating to attendance at foot monitoring clinics in a hospital outpatient clinic, primary care, or other community setting. Study dates March 2009 to Dec 2017 Sources of funding This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme (project no: HTA 15/171/01).

Inclusion criteria	Criteria 1 Patients who had received a diagnosis of diabetes and who attended a foot screening clinic between 2009 and 2017.
Number of participants	26,154
Loss to follow-up	Not reported, but if the only record for a patient in the data set was of their death (and hence no risk assessment data), that patient was excluded from the analysis cohort, so final analysis cohort was 26,086.
Duration of follow-up	8 years

Population baseline characteristics

Study-level characteristics

Characteristic	**Study (N = 26086)**
% Female Sample size	n = 12101 ; % = 46
Mean age (SD) Mean (SD)	68 (14)
Developed an ulcer during follow-up period No of events	n = 980 ; % = 3.8
Required an amputation during follow-up period No of events	n = 286 ; % = 1.1
Died during follow-up period	n = 6213 ; % = 23.8

Characteristic	Study (N = 26086)
No of events	

Appendix E – GRADE tables

F.1 Risk assessment tools

F.1.1 Prognostic accuracy measures for development of DFU

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Chen 2021 model: cut-off score of ≥ 46.5										
1 (Chen 2021)	Retrospective cohort	465	0.769 (not reported)	0.798 (not reported)	LR+ (not reported)	Serious[1]	Not serious	N/A[2]	N/A[3]	Moderate
					LR- (not reported)	Serious[1]	Not serious	N/A[2]	N/A[3]	Moderate
American Diabetes Association (ADA): high risk group										
1 (Monteiro-Soares 2017)	Prospective cohort	446	0.72 (0.56-0.87)	0.87 (0.84-0.90)	LR+ 5.6 (4.0-7.8)	Very serious[4]	Not serious	N/A[2]	Not serious	Low
					LR- 0.3 (0.2-0.6)	Very serious[4]	Not serious	N/A[2]	Serious[5]	Very low
American Diabetes Association (ADA): high and moderate risk group										
1 (Monteiro-Soares 2017)	Prospective cohort	446	0.84 (0.72-0.97)	0.77 (0.72-0.81)	LR+ 3.6 (2.9-4.5)	Very serious[4]	Not serious	N/A[2]	Not serious	Low
					LR- 0.2 (0.09-0.5)	Very serious[4]	Not serious	N/A[2]	Serious[5]	Very low
American Diabetes Association (ADA): high, moderate and low risk group										
1 (Monteiro-Soares 2017)	Prospective cohort	446	0.94 (0.85-1.00)	0.50 (0.45-0.55)	LR+ 1.9 (1.7-2.1)	Very serious[4]	Not serious	N/A[2]	Serious[6]	Very low
					LR- 0.1 (0.03-0.5)	Very serious[4]	Not serious	N/A[2]	Serious[5]	Very low
IWGDF: 3A + 3B										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Monteiro-Soares 2017)	Prospective cohort	446	0.72 (0.56-0.87)	0.87 (0.84-0.90)	LR+ 5.5 (4.0-7.6)	Very serious[4]	Not serious	N/A[2]	Not serious	Low
					LR- 0.3 (0.2-0.6)	Very serious[4]	Not serious	N/A[2]	Serious[5]	Very low
IWGDF: 3A + 3B + 2A + 2B										
1 (Monteiro-Soares 2017)	Prospective cohort	446	0.91 (0.81-1.00)	0.62 (0.58-0.67)	LR+ 2.4 (2.0-2.8)	Very serious[4]	Not serious	N/A[2]	Not serious	Low
					LR- 0.2 (0.05-0.4)	Very serious[4]	Not serious	N/A[2]	Not serious	Low
IWGDF: 3A + 3B + 2A + 2B + 1										
1 (Monteiro-Soares 2017)	Prospective cohort	446	0.94 (0.85-1.00)	0.50 (0.45-0.54)	LR+ 1.9 (1.6-2.1)	Very serious[4]	Not serious	N/A[2]	Serious[6]	Very low
					LR- 0.2 (0.05-0.4)	Very serious[4]	Not serious	N/A[2]	Not serious	Low
Seattle (refined): Highest risk										
1 (Monteiro-Soares 2017)	Prospective cohort	446	0.38 (0.17-0.59)	0.96 (0.94-0.98)	LR+ 10.2 (4.7-21.8)	Very serious[4]	Not serious	N/A[2]	Not serious	Low
					LR- 0.6 (0.5-0.9)	Very serious[4]	Not serious	N/A[2]	Serious[5]	Very low
Seattle (refined): Highest and next-to-highest										
1 (Monteiro-Soares 2017)	Prospective cohort	446	0.71 (0.52-0.91)	0.88 (0.84-0.91)	LR+ 5.8 (3.9-8.5)	Very serious[4]	Not serious	N/A[2]	Not serious	Low
					LR- 0.3 (0.2-0.6)	Very serious[4]	Not serious	N/A[2]	Serious[5]	Very low
Seattle (refined): Highest and next-to-highest and next-to-lowest										
1 (Monteiro-Soares 2017)	Prospective cohort	446	0.95 (0.86-1.00)	0.36 (0.31-0.41)	LR+ 1.5 (1.3-1.7)	Very serious[4]	Not serious	N/A[2]	Not serious	Low
					LR- 0.1	Very serious[4]	Not serious	N/A[2]	Serious[5]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
					(0.02-0.9)					
SIGN: High risk										
1 (Monteiro-Soares 2017)	Prospective cohort	446	0.91 (0.81-1.00)	0.58 (0.53-0.63)	LR+ 2.2 (1.8-2.5)	Very serious[4]	Not serious	N/A[2]	Serious[6]	Very low
					LR- 0.2 (0.05-0.5)	Very serious[4]	Not serious	N/A[2]	Serious[5]	Very low
SIGN: High and medium risk										
1 (Monteiro-Soares 2017)	Prospective cohort	446	0.94 (0.85-1.00)	0.50 (0.45-0.54)	LR+ 1.9 (1.6-2.1)	Very serious[4]	Not serious	N/A[2]	Serious[6]	Very low
					LR- 0.1 (0.03-0.5)	Very serious[4]	Not serious	N/A[2]	Serious[5]	Very low
UTFRS: 3										
1 (Monteiro-Soares 2017)	Prospective cohort	446	0.31 (0.15-0.47)	0.98 (0.97-1.00)	LR+ 18.5 (7.5-45.3)	Very serious[4]	Not serious	N/A[2]	Not serious	Low
					LR- 0.7 (0.6-0.9)	Very serious[4]	Not serious	N/A[2]	Not serious	Low
UTFRS: 3 + 2										
1 (Monteiro-Soares 2017)	Prospective cohort	446	0.72 (0.56-0.87)	0.74 (0.70-0.79)	LR+ 2.8 (2.1-3.7)	Very serious[4]	Not serious	N/A[2]	Not serious	Low
					LR- 0.4 (0.2-0.7)	Very serious[4]	Not serious	N/A[2]	Serious[5]	Very low
UTFRS: 3 + 2 + 1										
1 (Monteiro-Soares 2017)	Prospective cohort	446	0.75 (0.60-0.90)	0.59 (0.54-0.64)	LR+ 1.8 (1.4-2.3)	Very serious[4]	Not serious	N/A[2]	Serious[6]	Very low
					LR- 0.4 (0.2-0.8)	Very serious[4]	Not serious	N/A[2]	Serious[5]	Very low

[1] Downgraded 1 level due to moderate risk of bias
[2] Single study; inconsistency not applicable
[3] Not possible to assess for imprecision without 95% confidence intervals
[4] Downgraded 2 levels due to high risk of bias

[5] Downgraded 1 level due to 95%CI crossing 1 clinical decision threshold (0.5 to 1)
[6] Downgraded 1 level due to 95%CI crossing 1 clinical decision threshold (1 to 2)

F.1.2 C-statistics

No. of studies	Study design	Sample size	C-statistic (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Chen 2021 model, median 27 months follow-up								
Chen 2021	Retrospective cohort	465	0.798 (0.738-0.858)	Serious[1]	Not serious	N/A[2]	Serious[3]	Low
PODUS CPR, 2 years follow-up								
Crawford 2020	Prospective cohort	3324	0.83 (0.79-0.87)	Not serious	Not serious	N/A[2]	Serious[3]	Moderate
ADA, median 2.25 years follow-up								
Monteiro-Soares 2017	Prospective cohort	446	0.86 (0.76-0.95)	Very serious[4]	Not serious	N/A[2]	Very serious[5]	Very low
IWGDF, median 2.25 years follow-up								
Monteiro-Soares 2017	Prospective cohort	446	0.86 (0.77-0.96)	Very serious[4]	Not serious	N/A[2]	Very serious[5]	Very low
Seattle refined (continuous), median 2.25 years follow-up								
Monteiro-Soares 2017	Prospective cohort	446	0.88 (0.81-0.96)	Very serious[4]	Not serious	N/A[2]	Serious[8]	Very low
Seattle refined (categorical), median 2.25 years follow-up								
Monteiro-Soares 2017	Prospective cohort	446	0.84 (0.74-0.93)	Very serious[4]	Not serious	N/A[2]	Very serious[5]	Very low
SIGN, median 2.25 years follow-up								
Monteiro-Soares 2017	Prospective cohort	446	0.75 (0.66-0.84)	Very serious[4]	Not serious	N/A[2]	Very serious[9]	Very low
UTFRS, median 2.25 years follow-up								
Monteiro-Soares 2017	Prospective cohort	446	0.77 (0.65-0.89)	Very serious[4]	Not serious	N/A[2]	Very serious[9]	Very low

[1] Downgraded 1 level due to moderate risk of bias

[2] Single study; inconsistency not applicable
[3] Downgraded 1 level due to 95% confidence interval crosses 2 categories of test classification accuracy, ranging from good to excellent accuracy (0.7 - <0.8 and 0.8 - <0.9)
[4] Downgraded 2 levels due to high risk of bias
[5] Downgraded 2 levels due to 95% confidence interval crosses 3 categories of test classification accuracy, ranging from good to outstanding accuracy (0.7 - <0.8 and 0.9 - <1.0)
[6] Downgraded 1 level due to <33.3% of weighted data from studies at high risk of bias
[7] Not downgraded for inconsistency as $I^2 = 0.0\%$
[8] Downgraded 1 level due to 95% confidence interval crosses 2 categories of test classification accuracy, ranging from excellent to outstanding accuracy (0.8 - <0.9 and 0.9 - <1.0)
[9] Downgraded 2 levels due to 95% confidence interval crosses 3 categories of test classification accuracy, ranging from adequate to excellent accuracy (0.6 - <0.7 and 0.8 - <0.9)

F.1.3 Calibration statistics

F.1.3.1 Calibration slope

No. of studies	Study design	Sample size	Calibration slope (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
PODUS CPR								
1 (Crawford 2020)	Prospective cohort	3324	1.139 (0.994 to 1.283)	Not serious	Not serious	N/A[1]	N/A[2]	High

[1] Single study; inconsistency not applicable
[2] Not possible to assess imprecision

F.1.3.2 Calibration intercept

No. of studies	Study design	Sample size	Calibration intercept (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
PODUS CPR								
1 (Crawford 2020)	Prospective cohort	3324	-0.059 (-0.431 to 0.314)	Not serious	Not serious	N/A[1]	N/A[2]	High

[1] Single study; inconsistency not applicable
[2] Not possible to assess imprecision

F.1.4 Population-based probability of ulcer at 2 years

No. of studies	Study design	Number of participants	Population-based probability (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
PODUS CPR score 0								
1 (Crawford 2020)	Prospective cohort	4646	0.024 (0.014 to 0.039)	Not serious	Not serious	N/A[1]	N/A[2]	High
PODUS CPR score 1								
1 (Crawford 2020)	Prospective cohort	2406	0.060 (0.035 to 0.095)	Not serious	Not serious	N/A[1]	N/A[2]	High
PODUS CPR score 2								
1 (Crawford 2020)	Prospective cohort	676	0.140 (0.085 to 0.213)	Not serious	Not serious	N/A[1]	N/A[2]	High
PODUS CPR score 3								
1 (Crawford 2020)	Prospective cohort	358	0.292 (0.192 to 0.410)	Not serious	Not serious	N/A[1]	N/A[2]	High
PODUS CPR score 4								
1 (Crawford 2020)	Prospective cohort	169	0.511 (0.379 to 0.641)	Not serious	Not serious	N/A[1]	N/A[2]	High

[1] Single study; inconsistency not applicable
[2] Not possible to assess imprecision

F.1.5 Risk ratios for developing DFU

No. of studies	Study design	Sample size	Risk ratio (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Chen 2021 model; low-intermediate risk group vs low risk group								
Chen 2021	Retrospective cohort	465	1.50 (0.41 to 5.44)	Serious[1]	Not serious	N/A[2]	Very serious[3]	Very low
Chen 2021 model; high-intermediate risk group vs low risk group								
Chen 2021	Retrospective cohort	465	17.23 (5.12 to 58.02)	Serious[1]	Not serious	N/A[2]	Not serious	Moderate
Chen 2021 model; high risk group vs low risk group								
Chen 2021	Retrospective cohort	465	21.75 (5.16 to 91.74)	Serious[1]	Not serious	N/A[2]	Not serious	Moderate

[1] Downgraded 1 level due to moderate risk of bias
[2] Single study; inconsistency not applicable
[3] Downgraded 2 levels; 95% confidence interval crosses line of no effect and 1MID

F.2 Frequency of foot review

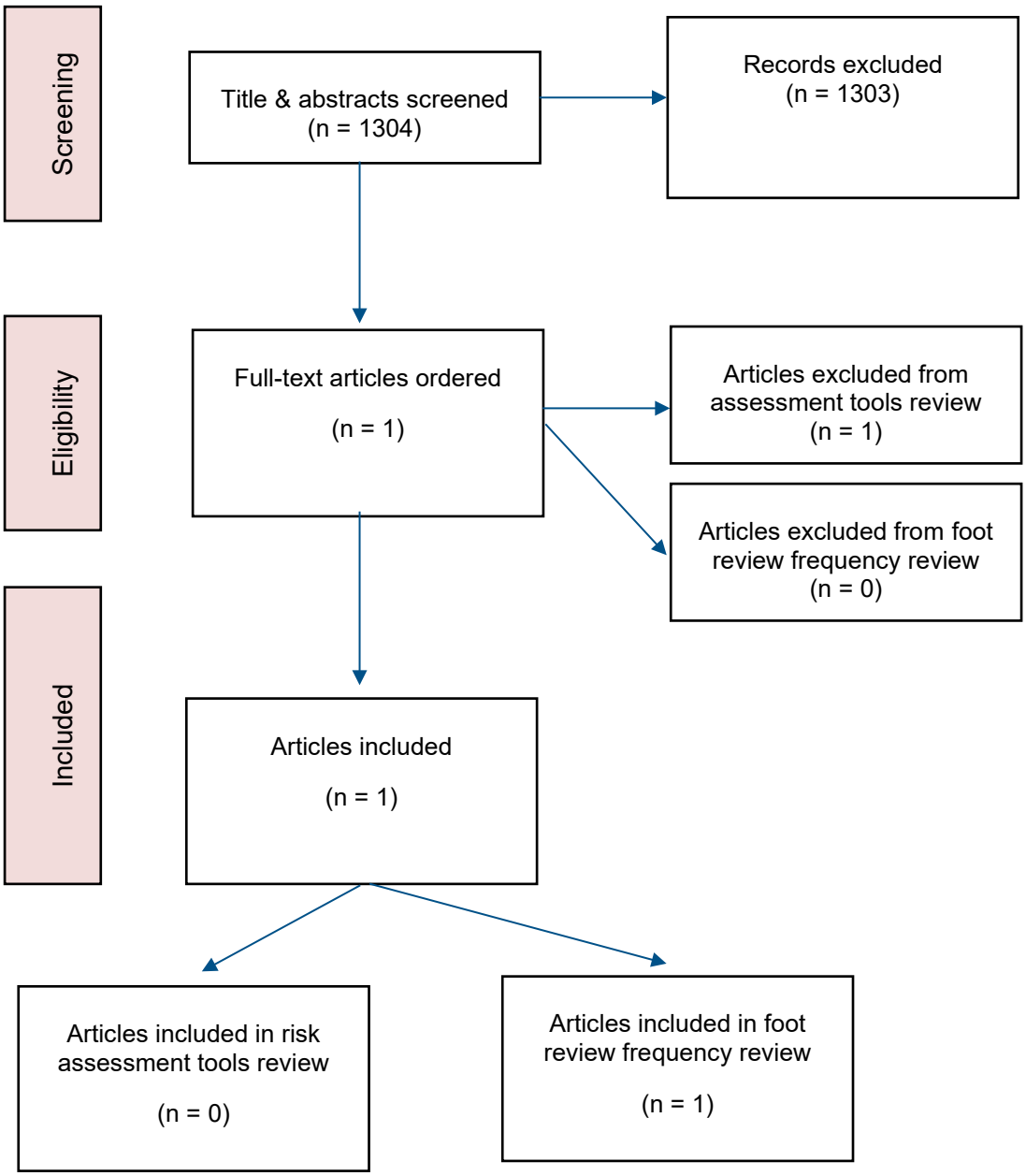
F.2.1 Incidence rates of transition from low to moderate risk status (per 1000)

No. of studies	Study design	Events	Incidence rate (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Transition period 0-1 year								
Heggie 2020 (subsample of Crawford 2020)	Retrospective cohort	172	18.14 (15.62, 21.07)	Not serious	Not serious	N/A[1]	N/A[2]	High
Transition period 1-2 years								
Heggie 2020 (subsample of Crawford 2020)	Retrospective cohort	313	34.81 (31.16, 38.88)	Not serious	Not serious	N/A[1]	N/A[2]	High
Transition period 2-3 years								
Heggie 2020 (subsample of Crawford 2020)	Retrospective cohort	180	23.06 (19.92, 26.69)	Not serious	Not serious	N/A[1]	N/A[2]	High
Transition period 3-4 years								
Heggie 2020 (subsample of Crawford 2020)	Retrospective cohort	114	17.94 (14.93, 21.55)	Not serious	Not serious	N/A[1]	N/A[2]	High
Transition period 4-5 years								
Heggie 2020 (subsample of Crawford 2020)	Retrospective cohort	51	10.30 (7.83, 13.56)	Not serious	Not serious	N/A[1]	N/A[2]	High
Transition period 5-6 years								
Heggie 2020 (subsample of Crawford 2020)	Retrospective cohort	43	11.76 (8.72, 15.86)	Not serious	Not serious	N/A[1]	N/A[2]	High
Transition period 6-7 years								
Heggie 2020 (subsample of Crawford 2020)	Retrospective cohort	11	4.63 (2.56, 8.37)	Not serious	Not serious	N/A[1]	N/A[2]	High

No. of studies	Study design	Events	Incidence rate (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Transition period 7-8 years								
Heggie 2020 (subsample of Crawford 2020)	Retrospective cohort	0	0	Not serious	Not serious	N/A[1]	N/A[2]	High
Transition period > 8 years								
Heggie 2020 (subsample of Crawford 2020)	Retrospective cohort	0	0	Not serious	Not serious	N/A[1]	N/A[2]	High

[1] Single study, inconsistency not applicable
[2] Not possible to assess imprecision

Appendix F – Economic evidence study selection



One study was included for both review questions after the title and abstract screening. After full text screening this study for excluded for the assessment tool review question because there was no cost effectiveness evidence which answered this question. The paper was included for the foot review frequency question only.

Appendix G – Economic evidence tables

Table 4: Economic evidence table

Reference: Crawford et al 2020 Risk assessments and structured care interventions for prevention of foot ulceration in diabetes: development and validation of a prognostic model	
Study details	**Analysis:** Cost utility analysis **Approach to analysis:** Markov model with 8 health states, low risk, medium risk, high risk, moderate risk plus treatment, high risk plus treatment, ulceration, amputation, and death **Perspective:** NHS and PSS **Time horizon:** 20 years **Discounting:** 3.5%
Interventions	The analysis explored the cost effectiveness of monitoring patients at different intervals. Patients in either the moderate or high risk categories were assumed to receive one of three preventative treatments (custom made footwear, digital infrared thermometry and complex interventions delivered by a multidisciplinary team). Only the results for patients treated with custom made footwear were included as this is the only intervention currently recommended by NICE and this review question is based on monitoring frequency and not preventative measures. **Intervention 1:** Current practice - current practice defined by natural history of disease and no use of prediction tool **Intervention 2:** Monitor every 2 years **Intervention 3:** Monitor annually **Intervention 4:** Monitor every 6 months **Intervention 5:** Treat all
Population	**Population:** Patients with diabetes who are attending a foot clinic in Fife **Characteristics:** Baseline age of 68 years old, 54% of the population were men. 96% of patients low risk (n=23,867), 3 % patients moderate risk and 1% patients high risk
Data sources	**Resource use:** Based on treatment strategy. **Baseline/natural history:** NHS Fife Scottish care information diabetes collaboration data set. This data set includes information across NHS fife foot monitoring clinics over a 12-year period, and contains patient records of routine management, patients were risk assessed using the SIGN classification system. **Effectiveness:** Sourced from the NHS Fife Scottish care information diabetes collaboration data set, outcomes assessed were changes in risk score and the number of amputations or ulcerations. **Costs:** BNF (NICE) and reference costs. **Quality of life:** Utilities sourced from the literature (Redekop et al 2004)
Base-case results	Current practice: Absolute costs £290, Absolute QALYs 6.791 Monitoring every 2 years versus current practice: absolute costs £423, absolute QALYs 6.804, incremental costs £133, incremental QALYs 0.013, ICER extendedly dominated, Incremental net monetary benefit (INMB) £120.39

Reference: Crawford et al 2020 Risk assessments and structured care interventions for prevention of foot ulceration in diabetes: development and validation of a prognostic model	
	Monitoring annually versus current practice: absolute costs £520, absolute QALYs 6.805, incremental costs £230, incremental QALYs 0.014, ICER extendedly dominated, Incremental net monetary benefit (INMB) £43.16 Monitoring every 6 months versus current practice: absolute costs £708, absolute QALYs 6.805, incremental costs £418, incremental QALYs 0.014, ICER extendedly dominated, Incremental net monetary benefit (INMB) £-134.25 All patients treated versus current practice: absolute costs £999 absolute QALYs 6.865, incremental costs £709, incremental QALYs 0.074, ICER £9,615, Incremental net monetary benefit (INMB) £765.91
Sensitivity analyses	**Deterministic:** Only the willingness to pay threshold and prevention treatment was varied as part of the one-way sensitivity analysis. **Probabilistic:** A probabilistic sensitivity analysis (PSA) was conducted by assigning a specific probability distribution for each of the key model inputs and running 1,000 simulations of the model results. Large uncertainty associated with the QALYs for each strategy, making it unclear which strategy had the greatest probability of being cost effective at a threshold of £20,000 per QALY. In the scenario of being treated with digital infrared thermometry (not recommended by NICE) there is approximately a 30% probability of being the most cost effective strategy at a willingness to pay threshold of £20,000 per QALY.
Comments	**Source of funding:** NIHR **Applicability:** Partially applicable **Limitations:** Minor limitations 1) The analysis did not explore different monitoring strategy by risk group as based on the CPR, the risk group was only used to determine whether preventative treatment was required. 2) The analysis did not include the strategy to increase monitoring to every 1-2 months for those patients at high risk, as currently recommended by NICE. However, the authors note that only 5% of patients changed status over 8 years and highlighted they would not expect enough events to be identified to offset the additional costs associated with more frequent monitoring. 3) Custom made footwear was the only preventative measure included in the review since it is currently recommended by NICE 4) Not a complete incremental analysis all monitoring frequencies compared to standard care

Table: 5 Economic evaluation checklist

Crawford et al 2020 Risk assessments and structured care interventions for prevention of foot ulceration in diabetes: development and validation of a prognostic model		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	

Crawford et al 2020 Risk assessments and structured care interventions for prevention of foot ulceration in diabetes: development and validation of a prognostic model		
Category	**Rating**	**Comments**
1.2 Are the interventions appropriate for the review question?	Partly	Current practice, monitor every 2 years, monitor annually, monitor every 6 months, treat all Current practice defined by natural history of disease and no use of prediction tool, whereas current NICE recommendations are by risk classification: Low risk: annually Moderate risk: frequently (every 3-6 months) High risk, no immediate concern: more frequently (every 1-2 months)
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK (evidence from Scotland)
1.4 Is the perspective for costs appropriate for the review question?	Yes	NHS and PSS
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	partly	Utility estimates obtained from the literature (Redekop et al.2004). These were from general population in the Netherlands
1.8 OVERALL JUDGEMENT	**PARTIALLY APPLICABLE**	There is no need to use section 2 of the checklist if the study is considered 'not applicable'.
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	partly	20 years
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	NHS Fife Scottish care information: Patients attending foot monitoring clinics, note there

Crawford et al 2020 Risk assessments and structured care interventions for prevention of foot ulceration in diabetes: development and validation of a prognostic model		
Category	**Rating**	**Comments**
		may be some variations in care in Scotland compared to England
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Only the willingness to pay threshold and prevention treatment was varied as part of the one-way sensitivity analysis. In probabilistic sensitivity analysis only, three scenarios were presented based on different treatment interventions (custom made footwear and offloading, digital infrared thermometry and complex interventions). Only the specialist footwear is recommended by NICE.
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

Appendix H – Health economic model

Economic modelling was not prioritised for this review question.

Appendix I – Excluded studies

Clinical studies

Study	Code [Reason]
(2014) Screening and risk stratification for diabetic foot ulcers: a review of clinical effectiveness, cost-effectiveness, and guidelines (Structured abstract). Canadian Agency for Drugs and Technologies in Health (CADTH)	- Review article but not a systematic review
Aan de Stegge, Wouter B, Schut, Martijn C, Abu-Hanna, Ameen et al. (2021) Development of a prediction model for foot ulcer recurrence in people with diabetes using easy-to-obtain clinical variables. BMJ open diabetes research & care 9(1)	- Paper does not present a risk stratification model or assessment tool
Al-Mohaithef, Mohammed, Abdelmohsen, Sahar A, Algameel, Magda et al. (2022) Screening for identification of patients at high risk for diabetes-related foot ulcers: a cross-sectional study. The Journal of international medical research 50(3): 3000605221087815	- Identified risk factors for diabetic foot but did not present a risk stratification system
Alencar, A.M.P.G., Firmino, P.R.A., De Cassia Felix Reboucas, V. et al. (2018) Risk classification of diabetic foot and association between sociodemographic and clinical characteristics of the aged. Diabetology and Metabolic Syndrome 10(supplement1)	- Conference abstract
Ang, Gary Y; Yap, Chun Wei; Saxena, Nakul (2017) Effectiveness of Diabetes Foot Screening in Primary Care in Preventing Lower Extremity Amputations. Annals of the Academy of Medicine, Singapore 46(11): 417-423	- Paper does not present a risk stratification model or assessment tool *Compared LEA outcomes for patients who received foot screenings versus those who did not receive foot screenings*
Beulens, Joline W J, Yauw, Josan S, Elders, Petra J M et al. (2021) Prognostic models for predicting the risk of foot ulcer or amputation in people with type 2 diabetes: a systematic review and external validation study. Diabetologia 64(7): 1550-1562	- Systematic review - papers checked and only 2 meet inclusion criteria, both already included in review
Bus, S.A., van Netten, J.J., Lavery, L.A. et al. (2016) IWGDF guidance on the prevention of	- Not a relevant study design

Study	Code [Reason]
foot ulcers in at-risk patients with diabetes. Diabetes/Metabolism Research and Reviews 32(supplement1): 16-24	*This paper is a summary of the IWGDF recommendations; not a trial paper*
Cesar Ernesto, Lam-Chung, Nestor, Martinez Zavala, Raul, Ibarra-Salce et al. (2021) Comparison of Clinical Tests for Peripheral Diabetic Neuropathy in a Type 1 Diabetes Cohort. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 27(6): 567-570	- Not a relevant study design *Cross-sectional study. Study examined the associations between several tools for testing sensory neuropathy but did not test their ability to predict DFU.*
Chang, Chia-Hao, Peng, Yun-Shing, Chang, Chang-Cheng et al. (2013) Useful screening tools for preventing foot problems of diabetics in rural areas: a cross-sectional study. BMC public health 13: 612	- Not a relevant study design *Cross-sectional study. Study examined the associations between several screening tools for diabetic foot but did not test their ability to predict outcomes.*
Chicharro-Luna, Esther, Pomares-Gomez, Francisco Jose, Ortega-Avila, Ana Belen et al. (2020) Predictive model to identify the risk of losing protective sensibility of the foot in patients with diabetes mellitus. International wound journal 17(1): 220-227	- Cross sectional study which developed a model to predict sensory peripheral neuropathy; not focused on diabetic foot ulceration
Choi, H.J. (2017) Comparison of five systems of classification of diabetic foot ulcers and predictive factors for amputation. Journal of Wound Care 26(suppl6): 299	- Examined ulcer classification systems rather than risk stratification systems
Crawford, F, Cezard, G, Chappell, F M et al. (2018) The development and validation of a multivariable prognostic model to predict foot ulceration in diabetes using a systematic review and individual patient data meta-analyses. Diabetic medicine : a journal of the British Diabetic Association 35(11): 1480-1493	- Meta-analysis of risk factors and preliminary development of CPR but not presented specifically as a risk stratification tool - precursor study to subsequent Crawford 2020 HTA
Crawford, Fay, Cezard, Genevieve, Chappell, Francesca M et al. (2015) A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS). Health technology	- Meta-analysis of risk factors and preliminary development of CPR but not presented specifically as a risk stratification tool - precursor study to subsequent Crawford 2020 HTA

Study	Code [Reason]
assessment (Winchester, England) 19(57): 1-210	
de Castro, J.P.W., Ferreira, F.C., Vargas, J.G.F. et al. (2021) Accuracy of Foot Pressure Measurement on Predicting the Development of Foot Ulcer in Patients with Diabetes: A Systematic Review and Meta-Analysis. Journal of Diabetes Science and Technology	- Paper does not present a risk stratification model or assessment tool
Dunn, G., Lunt, M., Rutter, M. et al. (2018) Developing a foot ulcer risk algorithm: The reality of doing this in a real world primary care setting. Diabetologia 61(supplement1): 474-s475	- Conference abstract
Edmonds, M., Robbie, J., Phillips, A. et al. (2021) A new diabetes foot educational and risk assessment tool for people with diabetes and health care professionals has been created: ACT NOW: Accident, Change, Temperature, New pain, Oozing, Wound, an acronym to recognise warning signs of foot complications, and reduce delays in much needed and timely specialist intervention(s) to avoid amputation. Diabetic Medicine 38(suppl1): 58	- Conference abstract
Eman, A. and Seamus, C. (2020) Risk assessment for foot ulcer in patients with type 2 diabetes presenting to the endocrine clinic: A descriptive study. Journal of Wound Care 29(suppl7b): 232	- Conference abstract
Farias Feitosa, Talita, Queiroz dos Santos Dantas, Moelisa, Brito da Silva, Cássia et al. (2016) Monofilament for preventing the diabetic foot: an integrative review of the literature. Online Brazilian Journal of Nursing 15(2): 291-301	- Review article but not a systematic review
Fernandez-Torres, R., Ruiz-Munoz, M., Perez-Panero, A.J. et al. (2020) Instruments of choice for assessment and monitoring diabetic foot: A systematic review. Journal of Clinical Medicine 9(2): 602	- Analysed psychometric properties of tools for diabetic foot assessment; did not test how well they predicted outcomes

Study	Code [Reason]
Fernandez-Torres, R., Ruiz-Munoz, M., Perez-Panero, A.J. et al. (2020) Clinician assessment tools for patients with diabetic foot disease: A systematic review. Journal of Clinical Medicine 9(5): 1487	- Reviewed and analysed psychometric properties of clinician assessment tools for DFU; did not examine their ability to predict development of DF
Foussard, Ninon, Saulnier, Pierre-Jean, Potier, Louis et al. (2020) Relationship Between Diabetic Retinopathy Stages and Risk of Major Lower-Extremity Arterial Disease in Patients With Type 2 Diabetes. Diabetes care 43(11): 2751-2759	- no mention of risk stratification or development of a tool. The paper is primarily interested in the prognostic performance of diabetic retinopathy which is out of scope.
Giacomozzi, Claudia, Sartor, Cristina D, Telles, Rafael et al. (2018) Ulcer-risk classification and plantar pressure distribution in patients with diabetic polyneuropathy: exploring the factors that can lead to foot ulceration. Annali dell'Istituto superiore di sanita 54(4): 284-293	- Examined the impact of plantar pressure distribution on ulcer-risk classification; did not present a risk assessment / classification system
Goldman, Matthew P, Corriere, Matthew A, Craven, Timothy et al. (2021) Evaluation of Neuropathy, Glycemic Control, and Revascularization as Risk Factors for Future Lower Extremity Amputation among Diabetic Patients. Annals of vascular surgery 73: 254-263	- Not a relevant study design *Randomised controlled trial*
Gonzalez-de la Torre, Hector, Quintana-Lorenzo, M Luana, Lorenzo-Navarro, Almudena et al. (2020) Diabetic foot self-care and concordance of 3diabetic foot risk stratification systems in a basic health area of Gran Canaria. Enfermeria clinica (English Edition) 30(2): 72-81	- Study not reported in English
Hangaard, Sine, Rasmussen, Anne, Almdal, Thomas et al. (2019) Standard complication screening information can be used for risk assessment for first time foot ulcer among patients with type 1 and type 2 diabetes. Diabetes research and clinical practice 151: 177-186	- Identified risk factors for diabetic foot but did not present a risk stratification system
Heald, A, Lunt, M, Rutter, M K et al. (2019) Developing a foot ulcer risk model: what is needed to do this in a real-world primary care	- Paper does not present a risk stratification model or assessment tool

Study	Code [Reason]
setting?. Diabetic medicine : a journal of the British Diabetic Association 36(11): 1412-1416	
Hippisley-Cox, Julia and Coupland, Carol (2015) Development and validation of risk prediction equations to estimate future risk of blindness and lower limb amputation in patients with diabetes: cohort study. BMJ (Clinical research ed.) 351: h5441	- Develops a model to classify subjects by their risk of lower extremity amputation; not DFU
Hu, A.; Koh, B.; Teo, M.-R. (2021) A review of the current evidence on the sensitivity and specificity of the Ipswich touch test for the screening of loss of protective sensation in patients with diabetes mellitus. Diabetology International 12(2): 145-150	- Outcome to be predicted do not match that specified in the protocol *Trial compared Ipswich touch test and 10g monofilament for assessing loss of protective sensation*
Hu, X., Xu, W., Shu, T. et al. (2017) Implementation of IWGDF risk classification in predicting the development of diabetic foot in type 2 diabetic patients admitted in the hospital: A three-year follow-up study. Diabetologia 60(1supplement1): 459	- Conference abstract
Husers, Jens, Hafer, Guido, Heggemann, Jan et al. (2022) Development and Evaluation of a Bayesian Risk Stratification Method for Major Amputations in Patients with Diabetic Foot Ulcers. Studies in health technology and informatics 289: 212-215	- Developed risk stratification method based on PEDIS classification to stratify patients with DFU into those with or without a risk for major amputation
Jiao, F, Fung, C S C, Wan, Y F et al. (2016) Effectiveness of the multidisciplinary Risk Assessment and Management Program for Patients with Diabetes Mellitus (RAMP-DM) for diabetic microvascular complications: A population-based cohort study. Diabetes & metabolism 42(6): 424-432	- Investigated the effects of a risk-stratification based diabetes management intervention compared with standard care on microvascular complications
Johnson, Rachel, Osbourne, Abe, Rispoli, Jessica et al. (2018) The Diabetic Foot Assessment. Orthopedic nursing 37(1): 13-21	- Not a relevant study design *Narrative review of diabetic foot assessments that nurses in healthcare settings should use*
Kleophas, W., Drozdz, M.B., Brzosko, S. et al. (2018) A european hemodialysis multicenter implementation of a standardized diabetic foot	- Examined the implementation of a standardised foot examination protocol, but did not present a risk stratification model or tool

Study	Code [Reason]
examination protocol. Journal of the American Society of Nephrology 29: 778-779	- Conference abstract *Poster presentation*
Kress, S., Anderten, H., Borck, A. et al. (2020) Preulcerous Risk Situation in Diabetic Foot Syndrome: Proposal for a Simple Ulcer Prevention Score. Journal of Diabetes Science and Technology 15(4): 816-826	- Paper does not present any data to test or validate the proposed scoring system
Lavery, Lawrence A, Petersen, Brian J, Linders, David R et al. (2019) Unilateral remote temperature monitoring to predict future ulceration for the diabetic foot in remission. BMJ open diabetes research & care 7(1): e000696	- Paper does not present a risk stratification model or assessment tool
Lee, E.J., Jeong, I.S., Kim, I.J. et al. (2021) Risk assessment and classification for foot ulceration among patients with type 2 diabetes in South Korea. International journal of nursing practice: e13012	- Not a relevant study design *Cross-sectional study assessing agreement between risk classification systems*
Li, Chia-Ing, Lin, Cheng-Chieh, Cheng, Hui-Man et al. (2020) Derivation and validation of a clinical prediction model for assessing the risk of lower extremity amputation in patients with type 2 diabetes. Diabetes research and clinical practice 165: 108231	- Developed a risk score system for lower extremity amputation, not diabetic foot ulcer
Madanat, Amal, Sheshah, Eman, Badawy, El-Badry et al. (2015) Utilizing the Ipswich Touch Test to simplify screening methods for identifying the risk of foot ulceration among diabetics: The Saudi experience. Primary care diabetes 9(4): 304-6	- Not a relevant study design *Cross-sectional observational study designed to test the accuracy of the Ipswich Touch Test against other tests of diabetic peripheral polyneuropathy*
Manu, Chris Adusei, Slim, Hani, Huang, Dean et al. (2021) Isolated low toe-brachial index is associated with increased mortality and morbidity: a retrospective cohort study. Journal of wound care 30(1): 65-73	- Population was patients with existing DFU *This study sought to assess the prognostic impact of toe-brachial index and ankle-brachial index for the diagnosis of PAD - this is out of scope as not focused on a risk stratification system for diabetic foot ulcer*

Study	Code [Reason]
Monteiro-Soares, M., Boyko, E.J., Jeffcoate, W. et al. (2020) Diabetic foot ulcer classifications: A critical review. Diabetes/Metabolism Research and Reviews 36(s1): e3272	- Examined ulcer classification systems rather than risk stratification systems
Monteiro-Soares, M and Dinis-Ribeiro, M (2016) A new diabetic foot risk assessment tool: DIAFORA. Diabetes/metabolism research and reviews 32(4): 429-35	- Develops a model to classify subjects by their risk of lower extremity amputation; not DFU
Monteiro-Soares, M, Martins-Mendes, D, Vaz-Carneiro, A et al. (2014) Classification systems for lower extremity amputation prediction in subjects with active diabetic foot ulcer: a systematic review and meta-analysis. Diabetes/metabolism research and reviews 30(7): 610-22	- Examined ulcer classification systems rather than risk stratification systems
Naemi, R, Chatzistergos, P, Suresh, S et al. (2017) Can plantar soft tissue mechanics enhance prognosis of diabetic foot ulcer?. Diabetes research and clinical practice 126: 182-191	- Paper does not present a risk stratification model or assessment tool
Ng, Chuan Guan, Cheong, Cherry Ya Wen, Chan, Wan Chin et al. (2022) Diagnostic thresholds for absolute systolic toe pressure and toe-brachial index in diabetic foot screening. Annals of the Academy of Medicine, Singapore 51(3): 143-148	- Paper focuses on assessment of DPN rather than risk assessment for DFU
Panagoulias, Georgios S, Eleftheriadou, Ioanna, Papanas, Nikolaos et al. (2020) Dryness of Foot Skin Assessed by the Visual Indicator Test and Risk of Diabetic Foot Ulceration: A Prospective Observational Study. Frontiers in endocrinology 11: 625	- Paper does not present a risk stratification model or assessment tool
Peng, Bocheng, Min, Rui, Liao, Yiqin et al. (2021) Development of Predictive Nomograms for Clinical Use to Quantify the Risk of Amputation in Patients with Diabetic Foot Ulcer. Journal of diabetes research 2021: 6621035	- Presents model to predict risk of amputation in people with DFU; does not provide model for predicting risk of DFU. Paper also uses the same sample for model development and validation.
Perez-Panero, Alberto J, Ruiz-Munoz, Maria, Cuesta-Vargas, Antonio I et al. (2019)	- Not a relevant study design

Study	Code [Reason]
Prevention, assessment, diagnosis and management of diabetic foot based on clinical practice guidelines: A systematic review. Medicine 98(35): e16877	*Systematic review of clinical practice guidelines, not research studies*
Richard, Jean-Louis, Reilhes, Lise, Buvry, Stephanie et al. (2014) Screening patients at risk for diabetic foot ulceration: a comparison between measurement of vibration perception threshold and 10-g monofilament test. International wound journal 11(2): 147-51	- Compared the accuracy of using 2 different methods for assessing loss of foot protective sensation. Did not present either method as a tool for stratifying risk of DFU
Rinkel, Willem D; Castro Cabezas, Manuel; Coert, J Henk (2021) A new application of the Rotterdam Diabetic Foot Study Test Battery: grading pedal sensory loss to predict the risk of foot ulceration. Diabetes research and clinical practice 175: 108836	- Tests an alternative method for assessing foot sensation other than 10g monofilament, but does not present a risk stratification system or tool for classifying risk of developing a DFU
Rismayanti, I.D.A., Nursalam, Farida, V.N. et al. (2022) Early detection to prevent foot ulceration among type 2 diabetes mellitus patient: A multi-intervention review. Journal of Public Health Research 11(2): 2752	- Review article but not a systematic review *Narrative review of methods for assessing risk of DFU (physical assessment, 3D thermal camera, screening instrument)*
Sanz-Corbalan, Irene, Lazaro-Martinez, Jose Luis, Garcia-Morales, Esther et al. (2018) Advantages of early diagnosis of diabetic neuropathy in the prevention of diabetic foot ulcers. Diabetes research and clinical practice 146: 148-154	- Diagnostic accuracy study comparing accuracy of sudomotor function test against 10g monofilament and biothesiometer measurements for assessing diabetic neuropathy
Sarinnapakorn, Veerasak, Sunthorntepwarakul, Thongkum, Deerochanawong, Chaicharn et al. (2016) Prevalence of Diabetic Foot Ulcers and Risk Classifications in Type 2 Diabetes Mellitus Patients at Rajavithi Hospital. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 99suppl2: 99-105	- Uses a Thai risk assessment system to study the prevalence of DFU but does not assess the predictive ability of that system to assess risk of developing DFU
Schafer, Z., Mathisen, A., Svendsen, K. et al. (2020) Toward Machine-Learning-Based Decision Support in Diabetes Care: A Risk Stratification Study on Diabetic Foot Ulcer and Amputation. Frontiers in Medicine 7: 601602	- Identified risk factors for diabetic foot but did not present a risk stratification system

Study	Code [Reason]
Schmidt, Brian M, Munson, Michael E, Rothenberg, Gary M et al. (2020) Strategies to reduce severe diabetic foot infections and complications during epidemics (STRIDE). Journal of diabetes and its complications 34(11): 107691	- Not a relevant study design *Longitudinal study of electronic medical records. Paper also does not present useable outcome data*
Selvarajah, Dinesh, Kar, Debasish, Khunti, Kamlesh et al. (2019) Diabetic peripheral neuropathy: advances in diagnosis and strategies for screening and early intervention. The lancet. Diabetes & endocrinology 7(12): 938-948	- Review article but not a systematic review
Sen, Pinar and Demirdal, Tuna (2021) Predictive ability of LRINEC score in the prediction of limb loss and mortality in diabetic foot infection. Diagnostic microbiology and infectious disease 100(1): 115323	- Population was patients with existing DFU *Study aimed to assess the effectiveness of a tool for predicting amputation or mortality in people hospitalised with a diabetic foot infection*
Sharma, S, Kerry, C, Atkins, H et al. (2014) The Ipswich Touch Test: a simple and novel method to screen patients with diabetes at home for increased risk of foot ulceration. Diabetic medicine : a journal of the British Diabetic Association 31(9): 1100-3	- Evaluated the use of the Ipswich Touch Test for use at home. Did not present a risk stratification tool or model
Shatnawi, Nawaf J, Al-Zoubi, Nabil A, Hawamdeh, Hasan et al. (2018) Redefined clinical spectra of diabetic foot syndrome. Vascular health and risk management 14: 291-298	- Population was patients with existing DFU
Shi, M., Steenhard, D., Dong, Y. et al. (2017) A predictive model to identify individuals with diabetes at high risk for developing foot wounds using administrative data and medical records. Diabetes 66(supplement1): a172	- Conference abstract
Shih, C.-D., Shin, L., D'Huyvetter, K. et al. (2020) Refocusing DFOCUS: An Update to the Diabetic Foot Online Clinic Utilization Score (DFOCUS) to Predict Clinic Volume. Journal of Diabetes Science and Technology 14(3): 671	- Conference abstract

Study	Code [Reason]
Soedamah-Muthu, Sabita S, Vergouwe, Yvonne, Costacou, Tina et al. (2014) Predicting major outcomes in type 1 diabetes: a model development and validation study. Diabetologia 57(11): 2304-14	- Outcome to be predicted do not match that specified in the protocol *Outcome was a composite score that comprised major outcomes (CHD, stroke, end-stage renal failure, amputations, blindness and death) - not possible to extract data for amputation only.*
Somayaji, Ranjani, Elliott, James A, Persaud, Reneeka et al. (2017) The impact of team based interprofessional comprehensive assessments on the diagnosis and management of diabetic foot ulcers: A retrospective cohort study. PloS one 12(9): e0185251	- Population was patients with existing DFU
Stotl, Iztok; Blagus, Rok; Urbancic-Rovan, Vilma (2022) Individualised screening of diabetic foot: creation of a prediction model based on penalised regression and assessment of theoretical efficacy. Diabetologia 65(2): 291-300	- Outcome to be predicted do not match that specified in the protocol
Tomita, M., Kabeya, Y., Okisugi, M. et al. (2015) Development and assessment of a simple scoring system for the risk of developing diabetic foot. Diabetology International 6(3): 212-218	- Tested a risk-based scoring system for determining which patients require further screening using the IWGDF system; did not present a clear risk stratification tool or system as the one proposed was for determining who should be assessed
Ugwu, Ejiofor; Anyanwu, Anthony; Olamoyegun, Michael (2021) Ankle brachial index as a surrogate to vascular imaging in evaluation of peripheral artery disease in patients with type 2 diabetes. BMC cardiovascular disorders 21(1): 10	- Not a relevant study design *Cross-sectional study*
van Doremalen, R F M, van Netten, J J, van Baal, J G et al. (2019) Validation of low-cost smartphone-based thermal camera for diabetic foot assessment. Diabetes research and clinical practice 149: 132-139	- Tested agreement between infrared thermal imaging using a high end IR camera or a smartphone-based camera. Did not present a model for using planar IR images of feet for predicting development of DFU
Weissler, E Hope, Clare, Robert M, Lokhnygina, Yuliya et al. (2021) Predicting major adverse limb events in individuals with type 2 diabetes: Insights from the EXSCEL trial. Diabetic medicine : a journal of the British Diabetic Association 38(10): e14552	- Outcome to be predicted do not match that specified in the protocol *Outcome was a composite of major adverse limb events (MALE), which included non-traumatic amputation, gangrene, and lower*

Study	Code [Reason]
	extremity revascularisation. Did not include infected ulcers.
Yunir, Em, Hidayah, Canggih Dian, Harimurti, Kuntjoro et al. (2022) Three Years Survival and Factor Predicting Amputation or Mortality in Patients with High Risk for Diabetic Foot Ulcer in Fatmawati General Hospital, Jakarta. Journal of primary care & community health 13: 21501319211063707	- Paper does not present a risk stratification model or assessment tool
Zantour, B, Bouchareb, S, El Ati, Z et al. (2020) Risk assessment for foot ulcers among Tunisian subjects with diabetes: a cross sectional outpatient study. BMC endocrine disorders 20(1): 128	- Not a relevant study design *Cross sectional study*
Zhao, N, Xu, J, Zhou, Q et al. (2021) Application of the Ipswich Touch Test for diabetic peripheral neuropathy screening: a systematic review and meta-analysis. BMJ open 11(10): e046966	- Diagnostic test accuracy review of Ipswich Touch Test for assessing diabetic peripheral neuropathy; not an included study type
Zhou, Qiuhong, Peng, Min, Zhou, Lihuan et al. (2018) Development and validation of a brief diabetic foot ulceration risk checklist among diabetic patients: a multicenter longitudinal study in China. Scientific reports 8(1): 962	- Presents a risk checklist tool but doesn't stratify patients into categories of risk and lacks detail of how to use this tool in practice

Economic evidence

Study	Code [Reason]
Crawford F, Chappell FM, Lewsey J, Riley R, Hawkins N, Nicolson D, et al. Risk assessments and structured care interventions for prevention of foot ulceration in diabetes: development and validation of a prognostic model. Health Technology Assessment 2020;24(62)	- Excluded from review question 1 because the interventions included within the analysis were based on prevention strategies rather than a comparison of monitoring tools.

Appendix J – Research recommendations – full details

J.1.1 Research recommendation

Based on clinical trial data and routinely collected real-world data, what is the clinical and cost-effectiveness of annual foot assessments for people categorised as low-risk compared to 2-yearly foot assessments in reducing diabetic foot problems (including ulcer, amputation and death)?

J.1.2 Why this is important

There remains uncertainty about whether diabetic foot screening prevents acute conditions and whether regular (annual or bi-annual) monitoring reduces people's risk of developing a diabetic foot problem. Some data has been collected but there is a need for further clinical trial evidence comparing the effectiveness and cost-effectiveness of annual foot assessments versus 2-yearly foot assessments for patients classified as low risk. In addition, there is a large potential resource of specific real-time outcome data that could be used to inform decision making about diabetic foot care.

J.1.3 Rationale for research recommendation

Importance to 'patients' or the population	The effectiveness of annual foot assessments in preventing ulceration has not yet been clearly established so both RCT data and routine healthcare data may be able to show the impact of foot check frequency on the subsequent occurrence of diabetic foot problems.
Relevance to NICE guidance	More robust clinical trial evidence is needed to determine whether the frequency of diabetic foot assessments can be changed. In addition, NICE is using more routine real-world healthcare data to assess the effectiveness of interventions, resolve gaps in knowledge and drive forward access to innovation for patients, so using clinical trial evidence in combination with real-world data will help further understand the impact of foot screening frequency.
Relevance to the NHS	With increasing numbers of people with diabetes, diabetic foot problems are also expected to increase, so understanding the rate of ulceration over time and the potential impact of foot check frequency could enable to NHS to better target resources toward those most at risk.
National priorities	High
Current evidence base	NICE does not have a current evidence base for diabetic foot assessments and ulcer occurrence using RCT trial data or routine healthcare data.

Equality considerations	By potentially reducing the frequency of foot assessments for those classified at low risk, greater access may be available for those hard-to-reach groups where take-up of foot assessments is lower. Using routine healthcare data will ensure a broader population is captured, rather than just those eligible for clinical trials.

J.1.4 Modified PICO table

Population	People with type 1 or type 2 diabetes who do not have an active foot ulcer at study baseline.
Intervention	Any other foot screening frequency
Comparator	Annual diabetic foot screen
Outcome	Ulceration, re-ulceration, osteomyelitis, gangrene, Charcot arthropathy, minor or major amputation, death.
Study design	RCT Routine healthcare data Registries / audits
Timeframe	Long term
Additional information	None

J.1.5 Research recommendation

What is the effectiveness, cost-effectiveness and acceptability of digital and emerging technologies for:

- assessing the risk of developing a diabetic foot problem
- helping to prevent diabetic foot problems from developing.

For example laser Doppler flowmetry, infrared thermography, and devices for measuring and providing feedback on plantar pressure.

J.1.6 Why this is important

There are several procedures and tools available for assessing various risk factors for diabetic foot (e.g. diabetic peripheral neuropathy, loss of protective sensation), and many new technologies are being developed to support their assessment. This includes devices to assess plantar tissue viability, infrared thermography for early detection of plantar tissue inflammation, plantar pressure and pressure gradient systems for identifying specific sites at risk for DFU, and continuous temperature monitoring socks. These devices may also help to prevent ulcers from developing. Evidence is needed to determine which is the most effective tool and whether it is acceptable to patients.

J.1.7 Rationale for research recommendation

Importance to 'patients' or the population	Diabetic foot screening can involve a number of different tests and assessments to determine a patients' risk of developing a foot ulcer. It is important to understand which method is most accurate, its acceptability to patients, and whether it can help to prevent ulcers from developing.
Relevance to NICE guidance	NICE is working to assess the effectiveness of many new digital interventions and technologies to drive forward access to innovation for patients.
Relevance to the NHS	Making the most of effective and efficient new technologies for foot screening could simplify the process, expand the number of health care professionals who are able to undertake foot screening, and improve screening accuracy. In some instances, it may facilitate patient self-monitoring or may allow for remote assessments. This could widen access to foot screening and help to better detect people at risk of developing a diabetic foot problem. These devices may also help to prevent ulcers from developing.
National priorities	High
Current evidence base	There is some evidence on various tools for assessing risk factors for diabetic foot, but it is unclear which tool is most effective and which patients find acceptable.
Equality considerations	Improving the acceptability of foot screening may increase access to diabetic foot assessments.

J.1.8 Modified PICO table

Population	People with type 1 or type 2 diabetes who do not have an active foot ulcer.
Intervention	Procedure, tool or technology for assessing risk factors for diabetic foot. (Example: 10g monofilament for assessing diabetic peripheral neuropathy; tools for assessing plantar pressure)
Comparator	Standard care or other method for assessing risk factors
Outcome	Ulceration Acceptability, patient experiences, views, preferences.

Study design	Mixed methods study – quantitative evidence on effectiveness of assessment tools and technologies, and qualitative evidence on patient acceptability of those tools.
Timeframe	Medium-term
Additional information	None

Appendix K – Methods

K.1.1 Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, from published systematic reviews) were uploaded into EPPI reviewer software version 5 and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies.

K.1.2 Data synthesis

Combining the evidence from univariate analyses (hazard ratios using the inverse-variance method, and odds ratios or risk ratios using the Mantel Haenszel method) using meta-analysis was not performed because the included studies did not report these outcome statistics. Furthermore, each of the included studies reported on different risk assessment tools so data could not be combined across studies. Results were reported narratively.

K.1.3 Appraising the quality of the evidence

Studies evaluating prediction models

Individual studies were assessed using the PROBAST checklist. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, predictor, or outcome to be predicted in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, predictor, or outcome to be predicted.
- Partially indirect – Important deviations from the protocol in one of the population, predictor, or outcome to be predicted.
- Indirect – Important deviations from the protocol in at least two of the population, predictor, or outcome to be predicted.

Modified GRADE for prediction models

GRADE has not been developed for use with data from prediction models or for prognostic reviews, therefore a modified approach was applied using the GRADE framework. The approach taken depended on the outcome data reported. Data from cohort studies was initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point. For rating risk of bias and indirectness, single studies were rated in the same way as meta-analysed studies, but with 100% of the weight in analysis contributed by that single study.

Clinical decision thresholds and assessing imprecision

The committee were asked to define clinical decision thresholds for association outcomes based on the degree of association that was considered clinically important for decision making. In cases where the committee were unable to define a clinical decision threshold, the line of no effect was used as the clinical decision threshold for the purpose of rating imprecision in GRADE.

For likelihood ratios (LRs), assessments for imprecision were based on 2 clinical decision thresholds: 2.0 for positive likelihood ratios and 0.5 for negative likelihood ratios. These decision thresholds were used with the line of no effect (1.0) to determine whether imprecision was not serious, serious (confidence interval crossing one threshold) or very serious (confidence interval crossing 1.0 and either 0.5 or 2).

For risk ratios, assessments for imprecision were based on the line of no effect (1.0) and default MIDs (0.8 and 1.25): outcomes were downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the effect estimate crossed either the line of no effect and one MID, or both MIDs (0.8 and 1.25).

Due to a lack of guidance and no obvious alternative method for assessing imprecision, ratings for imprecision were not provided for calibration statistics (calibration slope or intercept), population-based ulcer probability, and incidence rates of transition. These were marked as N/A in the GRADE tables and the overall quality rating was based on the remaining GRADE dimensions.

Table 6: Rationale for downgrading quality of evidence for association studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.

GRADE criteria	Reasons for downgrading quality
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity). This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.
Imprecision	If a clinical decision threshold other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the clinical decision threshold, and twice if it crosses both clinical decision thresholds. If the line of no effect was defined as a clinical decision threshold for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.
Publication bias	If the review team became aware of evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.

The quality of evidence for each outcome was upgraded if either of the following conditions were met:

- Data showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

K.1.4 Methods for combining c-statistics

C-statistics were assessed using the categories in Table 7 below.

Table 7 Interpretation of c-statistics

Value of c-statistic	Interpretation
c-statistic <0.6	**Poor classification accuracy**
0.6 ≤ c-statistic <0.7	**Adequate classification accuracy**
0.7 ≤ c-statistic <0.8	**Good classification accuracy**
0.8 ≤ c-statistic <0.9	**Excellent classification accuracy**
0.9 ≤ c-statistic < 1.0	**Outstanding classification accuracy**

Meta-analyses were carried out using the metamisc package in R v4.1.0, which confines the analysis results to between 0 and 1 matching the limited range of values that c-statistics can take. Random effects meta-analysis was used when the I^2 was 50% or greater.

K.1.5 Modified GRADE for c-statistics

A modified version of GRADE was carried out to assess the quality of the meta-analysed c-statistics as follows. For rating risk of bias and indirectness, single studies were rated in the same way as meta-analysed studies, but with 100% of the weight in analysis contributed by that single study.

Risk of bias

- Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded.
- Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level.
- Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.

Indirectness

- Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded.
- Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level.
- Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.

Inconsistency

Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic.

- N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study.
- Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded.
- Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level.

- Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.

Imprecision

The 95% CI boundaries were examined and if they crossed 2 categories of test classification accuracy then the study was downgraded once (imprecision rated as serious); if the boundaries crossed 3 categories then the study was downgraded twice (very serious imprecision).

In cases where meta-analyses could not be carried out due to single studies with or without 95% CI, the following decision rules were used to assess risk of bias, indirectness, imprecision and inconsistency for each outcome:

1. Risk of bias and indirectness were assessed as detailed above.
2. Imprecision
    - Single study with 95% CI: the 95% CI boundaries were examined and if they crossed 2 categories of test classification accuracy then the study was downgraded once (imprecision rated as serious); if the boundaries crossed 3 categories then the study was downgraded twice (very serious imprecision).
    - Single study without 95% CI: the mean sample size was calculated and if this was < 250 then the analysis was downgraded twice (very serious); if it was >250, but > 500 the analysis was downgraded once (serious); if the mean was > 500 people/study then the analysis was not downgraded (not serious).
3. Inconsistency
    - Single study with or without 95% CI: N/A.