Acceleration Award – Diabetic Foot Ulcer REsearch PlatFORM – DFU-REFORM

In line with the national priority of diabetes, addressing health inequalities and improving the care of people with co-morbid disease through multi-speciality research and underpinned by Patient and Public Involvement and Engagement (PPIE) and Equality, Diversity and Inclusion (EDI) we are seeking a 12-month NIHR HTA Acceleration Award. The award will enable enhancement of NHS and PPIE/EDI capacity and the design of a multi-disciplinary, adaptive diabetic foot ulcer (DFU) Platform Study which will aim to improve: diagnosis of adverse prognostic features e.g. infection or PAD; DFU treatment which maximises healing and minimises associated adverse sequelae; secondary prevention of recurrence of DFUs - to provide rapid and efficient delivery of research answering questions of importance to the NHS.

Background

Disease burden and costs: It is estimated that more than 4.9million UK adults have diabetes, with prevalence expected to rise to 5.5 million by 2030[1]. 25% of people with diabetes develop a DFU in their lifetime, and even after healing 40% will develop a recurrence within a year[2]. DFU treatment costs NHS England ~£1billion (2014/15)[3], with 60% of costs attributed to outpatient, community and primary care settings. The healthcare and patient burden will escalate in line with increased prevalence of obesity, diabetes and multi-morbidity (inc mental health). It is estimated that weekly treatment costs are £79 for mild/moderate ulcers and £242 for severe ulcers[3]. Assuming a 2% prevalence of DFUs in adults with diabetes[3] earlier healing of severe ulcers by just one week could save the NHS >£10million per year.

NICE guidelines (NG19) state that people with a DFU should be referred to a multidisciplinary team (MDT) service (comprising podiatry, diabetes care, vascular surgery, microbiology, orthopaedic surgery and orthotics) for triage within one working day[4]. Such **'MDT services'** comprise podiatry-led community-based services, hospital-based speciality podiatry and multi-disciplinary team (MDT) clinics in either a step-up or step-down pathway under the umbrella of a DFU 'MDT service'.

Less than half of (live) patients within the National Diabetic Foot Care Audit (NDFA) are ulcer free at 12 weeks from first expert assessment[5]. Delays in DFU healing increase risks of serious adverse events: tissue/bone infection; hospitalisation; amputation and mortality[6], increasing treatment costs and impacting adversely on patient health-related quality of life (HRQOL). Under-served populations include those with advanced age, low socio-economic status and minority ethnic populations. NB whilst BAME populations have a higher incidence of diabetes and are under-represented in trials/study populations and a key consideration in maximising accruals, they have a much lower prevalence of diabetic foot disease[7].

Current Strengths NIHR DFU Portfolio: Multi-speciality research spanning 'MDT services' is needed to improve the evidence base for clinical DFU treatment decision making. Since inception, NIHR has invested at least £10.5m through commissioned/responsive funding, with funding in the past 5 years providing for the first time, a clearly defined and complementary national portfolio of 2 trials (£3.5m), 2 programmes (£4.7m) and 4 Fellowships (£2.6m) with: critical multi-specialty clinical academic capacity and collaboration; research active 'MDT services' (re-emerging from COVID-19 impact); and committed PPIE contributors

Research Priorities: There has been investment from the Vascular Society in identifying research priorities through an inclusive James Lind Alliance (JLA) Priority Setting Partnership with 373 service users submitting 582 research questions across the vascular surgery spectrum which were grouped into 9 'conditions including 'diabetic foot', 'amputation' and 'wounds' [8] (see PPI section for more detail). This work has informed the proposed Acceleration Award platform design and priority clinical areas.

Capacity and capability of research delivery in DFU 'MDT services': The delivery of NIHR DFU studies has increased awareness of the role diabetes specialist podiatrists play in clinical research delivery within NHS DFU 'MDT services'.

Research delivery is most efficient where there are dedicated research podiatrists/assistants and specialist podiatrists providing local leadership. We need to further develop capacity and capability in research active centres, so that clinical research and standard care activities are integrated enabling efficient participant identification, screening, consent, intervention delivery and follow-up whilst minimising the impact/maximising the benefits of research on service delivery. This includes the need to

further support podiatry PIs and develop podiatry Associate PIs (an overlooked and important group), sharing business models and training the specialist podiatry clinical workforce.

Aim, Objectives and Work Packages (WPs)

Aim: Acceleration Award
Enhance NHS and PPIE/EDI capacity and design a multi-disciplinary adaptive DFU research platform study (DFU-REFORM) which will aim to improve DFU treatment which maximises healing and minimises associated adverse sequelae; and provide rapid and efficient delivery of research answering questions of importance to the NHS.

We have three Work-Packages (WPs) for the Acceleration Award:

Work-Package 1: DFU-REFORM NHS Centre Network/Enhanced Podiatry Capacity and Capability
Objective 1: Set-up a DFU-REFORM NHS Centre Network of 'research ready' DFU 'MDT services', with enhanced podiatry capacity and capability through: PI/Associate PI/team training; shared learning of effective approaches in research delivery; negotiation skills development to secure local resource; and clinical engagement in key aspects of platform design, definition/feasibility, baseline/outcomes data collection and trial interventions (see WP3).

Work-Package 2: PPIE and EDI, DFU-REFORM Service User Group
Objective 2: Set-up a Platform Service User Group to facilitate PPIE and EDI, providing the service user perspective and developing approaches to maximise research engagement of underserved populations underpinning all aspects of WP1 and WP3 Platform design and future Platform delivery.

Work-package 3: DFU-REFORM Study Application Development
Objective 3.1: Platform design – assess the feasibility and key design issues of a Platform Cohort design, with multiple embedded trials
Objective 3.2: Define the **platform cohort population**
Objective 3.3: Define and assess feasibility of **platform baseline and outcome dataset**
Objective 3.4: Design **3 diagnostic/intervention** trials including trial eligibility, interventions and trial specific baseline data and outcomes
Objective 3.5: Establish **statistical and economic analysis** arrangements
Objective 3.6: Establish **platform oversight/management/new intervention adoption** structures

Work-Package 1 NHS Podiatry Capacity and Capability/DFU-REFORM NHS Centre Network

DFU-REFORM NHS Centre Network*:* We will establish a national network of research ready NHS DFU 'MDT services', to enable rapid start-up of the Platform from April 2024. We have appraised current NHS Trust performance and identified NHS Trusts which fulfil 2 key criteria:

a) geographical location aligns to prevalence of DFUs and underserved populations (ie socio-economic, advanced age, ethnicity, rural vs urban) AND
b) research active 'MDT services' supporting existing NIHR portfolio study delivery, with strong MDT leadership and podiatry teams/Heads of Podiatry who have expressed a commitment to establishing a national network and enhancing research capacity and capability.

Platform design: Clinical team members of the DFU-REFORM NHS Centre Network will contribute to the development and feasibility assessment of key aspects of platform design, definition and clinical feasibility of baseline/outcomes data collection and trial interventions (see WP3).

Podiatry capacity/capability: We will work with participating Heads of Podiatry, Podiatry Specialists, established local PIs (Podiatrists/Vascular Surgeons/Diabetologists) and the Service User Group to:

1. Develop a group of DFU Specialist Podiatrists in trial delivery and as PI/Associate PIs.
2. Support/coach new PIs/Associate PIs and Heads of Podiatry in drafting business cases and securing integrated clinical research support (e.g. clinical research podiatrist/trial assistants)
3. Facilitate groupwork to share learning, DFU-REFORM Service User Group innovation and effective approaches in integrating screening, recruitment and follow-up within clinical delivery

4. Support PIs/Associate PIs in the development of podiatry team research capacity and capability including appraisal of the local screening/consent approaches and follow-up pathways.

We will work collaboratively with NIHR Clinical Research Network, Royal College of Podiatry and Diabetes UK, to ensure use of existing materials and sharing of new materials/lessons learned. Training, support and coaching will be delivered through face-to-face and virtual meetings/training events and site visits.

WP2 PPIE and EDI/ DFU-REFORM Service User Group

The Acceleration Award has been informed by the Vascular Society/JLA Research Priority Setting Partnership and co-produced with PPIE members with experience on DFU study oversight groups and/or as a service user.

Service User Involvement in Research Priority Setting
We have led a JLA priority setting partnership in DFUs with 373 service users submitting 582 research questions across the spectrum of vascular surgery which were grouped into 9 'conditions including 'diabetic foot', 'amputation' and 'wounds' [8]. In a topic specific second round of prioritisation, the top 10 priorities for 'diabetic foot' were identified at an online workshop of nine service users and nine clinicians. The work provided new insights into issues important to service users with diabetes and foot problems and priorities were focused on the primary prevention of ulcers, secondary prevention of recurrence after initial healing, questions which require an improved evidence base relating to prognostic factors for healing and how to improve outcomes for and minimise adverse sequelae (eg infection, amputation) [31]. In addition, the topic specific second round of prioritisation for 'wounds' (which considered both 'open' wounds and post-operative sutured surgical wounds) the priority ranked 2 of 10 was 'How can healing of open wounds be accelerated?' [8].

Pre grant work with our PPIE collaborators informed the development of WP2 and their proposed set up of a DFU-REFORM Service User Group and the scope of the involvement and engagement.

WP2 Objective: Set-up Platform Service User Group to facilitate PPIE/EDI, providing the service user perspective and developing approaches to maximise research engagement of underserved populations underpinning all aspects of WP1 and WP3.

DFU-REFORM Service User Group: We will bring together existing PPIE colleagues supporting the NIHR DFU portfolio and further develop membership using outreach approaches to ensure representativeness[32] [33] [34]. Using inclusive approaches to facilitate engagement and discussion the Group will play a key role in:

DFU-REFORM Inclusion/Diversity Assessment and Plan: will be developed informed by INVOLVE[34], Bodicoat[33], Trials Forge[35], INCLUDE Ethnicity Framework[36] and experience in previous studies.

Patient information and communications: This patient population have multiple comorbidities and complex needs which can affect ability to read, write and comprehend information, affecting inclusivity. We will:
a. Create accessible forms of patient information
b. Consider witnessed verbal consent approaches
c. Consider patient reported outcomes burden

Platform Design : The Service User Group members will be fully involved and provide the patient perspective in all aspects of platform design.

Training and support: Service User Members will have 1to1 induction meetings, including discussion to elicit: skills and experience; the support they may need and the variety of role/types of engagement activities; determine what activity best suits them and; support through accessible training. .

WP 3 DFU-REFORM Study Application Development

Objective 3.1: Platform design: A key element of WP3 is to identify the optimal design of a platform. Two options are of interest which both allow intervention trials including adaptive designs with embedded economic analysis.

Our preferred approach is Trials within Cohort (TWiC) [9] [10]. If this is not feasible, we will develop an Umbrella Platform which reduces data collection burden as only trial participants are recruited.

Justification for cohort: There has been no contemporary data on the natural history, treatments and outcomes of people with DFUs for 20 years (EURODIALE cohort study (n=1232, 2003-4, 14 European MDT clinics)[14]. Standard care has since progressed including: introduction of new assessment techniques and DFU classifications; new adjuvant therapies; advanced wound dressings; complex endovascular revascularisation techniques; minimally invasive surgery for infection and topical antibiotic eluting composites. Their impact has not been well characterised and all technologies assessed by NICE over the last 3 years have concluded that both higher quality evidence is required[15, 16] [17, 18], and that more detailed data on resource use associated with treatment of hard-to-heal DFUs would be valuable[17]. Additional fundamental questions in DFU care remain (see JLA priorities in PPIE section [8]), for example: benefits of early advanced/adjuvant therapies; benefit from revascularisation and; infection management strategies eg antibiotics alone vs antibiotics plus early surgery?

A cohort platform will enable us to maximise inclusivity and account for heterogeneity in patients, patient care and access to treatments and associations with outcomes. A large cohort study will enable us to better describe the natural history of DFUs through multi-state modelling (MSM) [19] i.e. healing, non-healing, deteriorating, healed and recurrence. With robust, prospective data collection, clinical prediction models and multi-state modelling may be developed to provide more personalised care and improved health economic models. Cohort data will better inform trial designs/sample size estimates and the use of MSMs in trial designs may allow reduced sample sizes[19].

Our main concern with a TWiC is the potential data collection burden for teams and the resources required to recruit circa 4000 patients per year and implement a minimum data collection standard as part of standard clinical practice, so we have planned a feasibility work (see 3.3 below).

Objective 3.2 Platform Population

The Cohort Platform patient population will align with the NDFA, corresponding to all patients with a first presentation of a new or recurring DFU. Participation in the embedded intervention trials will depend on the eligibility criteria for each individual trial. Two important components of the work with centres will be to: a) develop Platform procedures to identify patients as they progress through multiple potential states (eg healing, delayed healing, deterioration, healed and ulcer recurrence) so they can be flagged for recruitment and b) assess scientific and patient burden considerations for the recruitment of participants to multiple trials, as they progress through multiple states.

Objective 3.3: Platform baseline and outcome datasets

Platform Baseline Dataset:

Platform Outcome Dataset:

Feasibility: We will complete a gap analysis to identify podiatry/MDT skills development and any enhanced clinic equipment requirements for baseline cohort data. We will assess the feasibility of screening and remote data capture of baseline and outcome data by asking a minimum of 8 DFU-REFORM centres to complete baseline and a follow-up assessment on a target of 5 patients. Information recorded to inform feasibility will include time to complete data collection, source of data (ie clinical record or study specific assessment) and job role of the person collecting the data (eg clinical trial assistant, podiatrist). We don't anticipate feasibility of data collection to vary with patient heterogeneity and a minimum of 8 centres should provide a representative cross-section on the level of DFU clinical research activity and thereby feasibility of data collection in the proposed cohort.

We will work with our DFU-REFORM Service User Group to assess patient data burden of HRQOL questionnaires and ensure data collection methods maximise inclusion of under-represented groups.

Objective 3.4: PICO questions

We will build upon the previous research priority setting undertaken by the Vascular Society and James Lind Alliance (JLA) Priority Setting Partnership and the 2023 published guidelines of the International Working Group of the Diabetic Foot which include systematic reviews and evidence appraisal and identify research priorities. We will work through the research priorities with the NHS DFU-REFORM Centre Network podiatry colleagues and clinical co-applicants to identify a short-list of PICO questions based upon clinical pathways in the UK and associated feasibility, undertaking focused workshops to work through eligibility, interventions, trial primary and secondary outcomes (to inform sample size estimates) and consider feasibility and practicalities of a cohort design with embedded trials.

Trial specific baseline data and outcomes: assuming a Platform Cohort design, each trial sub-protocol will specify diagnostic/intervention specific baseline characteristics and outcomes. We anticipate that these will add minimal additional burden and could include for example diagnostic test results, intervention compliance, or mechanistic intervention outcomes such as resolution of infection.

3.5 Statistical and economic analysis arrangements

We will appraise statistical and health economic aspects of cohort and trial design including sample sizes for cohort analyses and trial control and intervention comparisons, interim analyses and stopping rules, issues of co-enrolment and analysis considerations. We will develop a master statistical analysis plan (SAP) and health economic analysis plan (HEAP) and a trial specific template to pre-define the statistical and health economic considerations for the proposed cohort and common considerations for diagnostic/intervention trials embedded within the cohort platform. A systematic review concluded that DFU health economic evaluations were so heterogeneous that comparison across studies were not possible [30]. To address this the HEAP will establish an optimal independent evaluation framework including which states and appropriate time perspective based on the drivers of cost and utility and natural history of patients. The economic output will include development of state-based utility values and resource use 'off the peg' standard resource for evaluations that do not use the platform. We will appraise an efficient database design model and assess statistical resource arrangements for the Platform Cohort and each embedded trial to maintain statistical oversight and conduct.

Objective 3.6: Platform oversight/management/new trial and intervention adoption structures

We will establish a master Platform Oversight Committee including a Chair with experience as Chief Investigator of a Platform/MAMS in a related field; develop new trial acceptance processes and; establish CI responsibilities and organisation for a Cohort Chief Investigator and a Chief Investigator or Co-Chief Investigators for each embedded trial.

Timelines, Project Management, Expertise, Collaborative Learning and Dissemination

Timelines:

M1: appoint DFU-REFORM Clinical Coordinator/initiate DFU-REFORM Management Group
M2: establish Service User Group membership, group forming meetings and agree workplan
M3: initiate training and group work with DFU-REFORM NHS Centre Network
M3-5: platform baseline and outcome datasets scoping reviews and rapid consensus
M6-7: platform feasibility assessment and trial design
M7: Oversight Committee Meeting; confirm charter and candidate technologies for embedded studies
M9: November 2023: Submit HTA Stage 1 application DFU-REFORM
M10: deliver innovative patient information and communications materials
M11: final delivery of DFU-REFORM NHS Centre Network training and development
M12: February 2024 Submit Stage 2 HTA application and finalise SAP/HEAP and outputs dissemination.

Dissemination: we will share learning through: a themed Wounds Research Network Scientific Meeting; Vascular and Diabetes national clinical meetings; methodological meetings eg MRC-NIHR Trials Methodology Research Partnership and the International Clinical Trials Methodology Conference and; PPIE forums. We will make patient information materials and clinical training materials available across existing portfolio study groups and through the Royal College Podiatrists and CRN and publish the rapid consensus work to maximise wider dissemination.