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Insoles to ease plantar pressure in people with diabetes and peripheral neuropathy: a feasibility randomised controlled study with embedded qualitative component

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http://hdl.handle.net/10026.1/17292

http://dx.doi.org/10.24382/466
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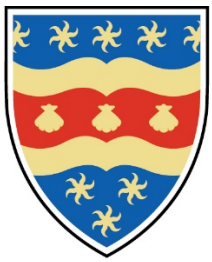

UNIVERSITY OF PLYMOUTH

Insoles to ease plantar pressure in people with diabetes and peripheral neuropathy: a feasibility randomised controlled study with embedded qualitative component

by

Richard Collings

A thesis submitted to the University of Plymouth in partial fulfilment for the degree of

Doctor of Philosophy

School of Health Professions

April 2021

Acknowledgements

Completing this thesis has been the culmination of a long, rewarding journey, one that would not have been possible without the collaboration and support of many people.

I am incredibly indebted to my supervisory team, whose wisdom, support and expertise have led me through this journey. Director of Studies Dr Joanne Paton, a magnificent role model who has shared her knowledge and support for many years; Professor Jennifer Freeman, whose attention to detail, honesty and encouragement has been enormously valuable; Professor Jos M Latour, whose positivity and challenging foresight always brought a calming influence. I will never forget the magnificent debates amongst the supervisory team and the belief they placed in me.

Sincere thanks and gratitude to all the participants, podiatrists and other clinical, administrative and research staff involved in the INSTEP study. A special mention to my colleague and friend, Dr Sam Glasser, whose patience and advice was always gratefully received. I am particularly grateful to the representatives who provided immense support and interest to the study throughout.

I gratefully acknowledge the National Institute for Health Research for funding my Clinical Doctoral Research Fellowship. The fellowship has been a precious opportunity, both professionally and personally.

Thank you to the Trial Management Group: Dr Joanne Paton, Professor Jennifer Freeman, Professor Jos M Latour, Dr Doyo Enki, Dr Joanne Hosking, Dr Helen Hancocks (RIP), Miss Jane Vickery and Mr Peter Gates. Special

thanks to Mr Jonny Wilkes, Data Manager, whose variety of passwords kept me entertained.

I sincerely appreciate the guidance and integrity of the Trial Steering Committee: Dr Joanne Paton, Dr Duncan Brown, Mrs Carol Greechan, Dr Joanne Hosking, Dr Natalie Rowlands. Special thanks to the Chair, Dr Richard Paisey, whose passion for improving diabetic foot services is genuinely remarkable, and Professor Siobhan Creanor for always keeping oversight.

I am very grateful to Professor Anne-Maree Keenan, University of Leeds, for her mentorship throughout my fellowship.

Finally, I would like to thank my family and friends who have provided enormous support and reassurance. In particular, my wife, daughter, and parents who gave me the belief to enable me to be where I am today. Thank you to you all.

Author's Declaration

At no time during the registration for the degree of Doctor of Philosophy has the author been registered for any other University award without the prior agreement of the Doctoral College Quality Sub-Committee.

Work submitted for this research degree at the University of Plymouth has not formed part of any other degree either at the University of Plymouth or at another establishment.

This trial was financed with the aid of a Clinical Doctoral Research Fellowship from the National Institute for Health Research (ICA-CDRF-2015-01-05) and supported by the School of Health Professions, Plymouth University.

A programme of advanced study was undertaken, which included methodological and speciality specific training.

Disclaimer: The content presents independent research funded by NIHR. The views expressed are those of the author(s) and not necessarily those of the National Health Service (NHS), the NIHR, or the Department of Health and Social Care.

Word count of the main body of the thesis: 58,567

Signed: Richard Collings

Date: 19th March 2021

Research Outputs

Publications in peer-reviews journals

Collings, R., Freeman, J., Latour, J. M. & Paton, J. (2020) 'Footwear and insole design features for offloading the diabetic at risk foot—A systematic review and meta-analyses.' *Endocrinology, diabetes & metabolism*, 10.1002/edm2.132p. e00132 DOI: 10.1002/edm2.132 [Online]. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/edm2.132 (Accessed: 2020).

Collings, R., Freeman, J. A., Latour, J., Vickery, P. J., Glasser, S., Lepesis, V., Enki, D. & Paton, J. (2019) 'INSoles To Ease Pressure (INSTEP) Study: a multicentre, randomised controlled feasibility study to compare the effectiveness of a novel instant optimised insole with a standard insole for people with diabetic neuropathy: a study protocol.' *BMJ Open*, 9 (3), p. e029185 DOI: 10.1136/bmjopen-2019-029185 [Online].

Collings, R., Freeman, J., Latour, J. M., Glasser, S. & Paton, J (2017). 'Footwear and insole design features to prevent foot ulceration in people with diabetes: A systematic review protocol.' *JBI Database of Systematic Reviews and Implementation Reports,* 15 (7), pp1824-1834.

Notable awards

South West AHP NIHR/CAHPR research champion 2018-present

Honorary Clinical Research Fellow (University of Plymouth) 2021-present

Conference abstracts and presentations

Collings, R., Freeman, J., Latour, J. M. & Paton, J. (2018). *Oral presentation at South West Clinical Schools Conference*. 'INSoles To Ease Pressure (INSTEP) Study: a multicentre, randomised controlled feasibility study to compare the effectiveness of a novel instant optimised insole with a standard insole for people with diabetic neuropathy: a study protocol.' 16th May 2018, Torbay, UK.

Collings, R., Freeman, J., Latour, J. M. & Paton, J. (2018). *Poster presentation at College of Podiatry Conference.* 'INSoles To Ease Pressure (INSTEP) Study: a multicentre, randomised controlled feasibility study to compare the effectiveness of a novel instant optimised insole with a standard insole for people with diabetic neuropathy: a study protocol.' 22-24th November 2018, Bournemouth, UK.

Collings, R., Freeman, J., Latour, J. M. & Paton, J. (2019). *Poster presentation at International Working Group for Diabetes*, Insoles To Ease Pressure (INSTEP): an offloading algorithm. 22-25th June 2019, The Hague.

Collings, R., Freeman, J. A., Latour, J. M. & Paton, J. (2019). *Oral presentation at Torbay Clinical School Conference.* 'Feedback from participants and clinicians on their experiences of the INSTEP feasibility study – implications for future clinical trial design for people with diabetes.' 15th October 2019, Torbay, UK.

Collings, R., Freeman, J. A., Latour, J. M. & Paton, J. (2019 *Oral presentation at College of Podiatry Annual Conference.* 'INSoles To Ease Pressure (INSTEP) Study: a multicentre, randomised controlled feasibility study to compare the effectiveness of a novel instant optimised insole with a standard insole for people with diabetic neuropathy: a study protocol.' 21-23rd November 2019, Harrogate, UK.

Abstract

Collings, R.

Insoles to ease plantar pressure in people with diabetes and peripheral neuropathy: a feasibility randomised controlled study with embedded qualitative component.

Background: Diabetic foot ulceration is a devastating complication of diabetic foot disease. Therapeutic footwear and insoles are one preventative strategy to reduce elevated plantar pressures associated with foot ulcer risk. However, their effectiveness is variable, difficult to predict and evaluated by the high-risk strategy of observing foot health and tissue integrity over time.

Aim: To develop and test, in a feasibility randomised controlled trial (fRCT), an insole prescription and fabrication intervention appropriate for chairside delivery to reduce plantar foot pressures and consequent foot ulceration risk in people with diabetes.

Methods: The Medical Research Council's framework for developing and evaluating complex interventions was adopted. The first phase developed the novel optimised insole intervention, informed by stakeholder and patient/public involvement and a systematic review with three meta-analyses. The second phase involved conducting a double-blinded multicentre fRCT with an embedded qualitative study. In addition to usual care, participants were randomised to either an optimised insole group or an active control group. Participants were assessed at baseline and then again at 3, 6 and 12 months with clinical outcomes of mean peak plantar pressure (MPPP) reduction for identified regions-of-interest and ulcer incidence. The embedded qualitative study involved semi-structured interviews with 12 study participants and three

podiatrists to explore their experiences of the intervention and trial procedures. Data were analysed using descriptive statistics (quantitative data) and thematic analysis (qualitative data).

Results: The systematic review identified the best footwear and insole design features for offloading the plantar surface of the foot to prevent foot ulceration in people with diabetic peripheral neuropathy. The review involved 54 studies, with random-effects modelling finding plantar pressure reductions with an arch profile (37kPa), metatarsal addition (36kPa) and with pressure informed design (75kPa). An optimised insole algorithm based on real-time temporal load and pressure profiles was created to underpin the optimised insole intervention.

The fRCT screened 142 participants from which 61 participants were recruited; 30 randomised to the optimised insole group and 31 to the active control insole group. Forty-two participants completed the study and at 12-months, 69% of patient-reported questionnaires were returned and 68% of clinical outcomes were collected. There were seven incidences of foot ulceration in the active control group and 10 in the optimised insole group. Mean difference in MPPP between the optimised insole and active control insole for all regions-of-interest combined favoured the optimised insole, with increases from 87kPa at post-randomisation to 255kPa at 12-months. Thematic analysis revealed three themes; accepting the study, behaviour and support during study procedures, and impact from study participation.

Conclusion: An optimised insole intervention has been developed to reduce the risk of foot ulceration in people with diabetic peripheral neuropathy. The feasibility study results suggest that the optimised insole holds promise as an

intervention and that a full RCT to evaluate the clinical and cost-effectiveness of this intervention is feasible and warranted for people with diabetic peripheral neuropathy.

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List of Abbreviations

AE	Adverse Event
BEUP	Balance Enhancement and Ulcer Prevention
CI	Chief Investigator
CMI	Custom Made Insole
CRN	Clinical Research Network
DFU	Diabetic Foot Ulceration
DM	Diabetes Mellitus
DPN	Diabetic Peripheral Neuropathy
fRCT	feasibility Randomised Controlled Trial
HRA	Health Research Authority
INSTEP	INSoles To Ease Pressure
ISRCTN	International Standard Randomised Controlled Trials Number
MPPP	Mean Peak Plantar Pressure
MRC	Medical Research Council
NHS	National Health Service
NIHR	National Institute for Health Research
PAD	Peripheral Arterial Disease
PenCTU	Peninsula Clinical Trials Unit
PI	Principal Investigator
PIS	Participant Information Sheet
PP	Peak Pressure
PPP	Peak Plantar Pressure
PTI	Pressure Time Integral
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
ROI	Regions of Interest
SAE	Serious Adverse Event
SD	Standard Deviation
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom

Chapter 1 Introduction

Diabetic foot ulceration (DFU) is a devastating multi-factorial complication of diabetes. At any one time, the National Diabetes Footcare Audit reports that approximately 64,000 people in the United Kingdom (UK) have a diabetic foot ulcer (Digital, 2018). It is considered one of the most common complications that leads to lower limb amputation, or even death in extreme cases. In 2014-2015, estimates of costs attributed directly to DFU and lower limb amputation in the National Health Service (NHS) in England was at £972m - £1.13 billion (Kerr, 2017). Increased personal and societal costs in terms of psychosocial and physical behaviours (Bonner, Foster & Spears-Lanoix, 2016) and reductions in quality of life (Goodridge, Trepman & Embil, 2005; Khunkaew, Fernandez & Sim, 2019) are also reported. The Global Burden of Disease study ranks Diabetes Mellitus (DM) related lower extremity complications as 10th on a scale of leading causes of global years lived with disability in 2015 (James *et al.*, 2018; Lazzarini *et al.*, 2018).

The most effective way to reduce the enormous burdens associated with ulceration is by prevention. Prevention of first diabetic foot ulcer or recurrence of DFU is achieved by a combination of strategies (Bus & van Netten, 2016). One preventative strategy is through the use of therapeutic footwear and insoles that have pressure-relieving effects. However, despite high-quality systematic review evidence that supports the use of therapeutic footwear and insoles to prevent DFU (Bus *et al.*, 2016; Paton *et al.*, 2011; van Netten *et al.*, 2016), there is substantial diversity and variation in efficacy (Crawford *et al.*, 2020), in design, and with frequent delays in delivery to patients. This uncertainty can

make the use of therapeutic footwear and insoles ill-timed, with difficulties in predicting effectiveness and evaluation for people at risk of DFU.

This thesis reports on the development of a novel optimised insole to reduce the risk of DFU for people with diabetic peripheral neuropathy (DPN). This work is important because of the need to find the best way of reducing the variability in therapeutic footwear and insoles for people with DPN. It is the first study testing the feasibility of an instant, optimised insole. The optimised insole contributes to original practice by being the first to use in-shoe plantar pressure analysis to inform its design using a standardised algorithm, based on walking gait patterns, provided at the same clinic appointment, using commercially available materials. The ultimate purpose of this work is to provide the necessary operational experience and preparatory data to inform the design and implementation of a definitive randomised controlled trial (RCT) to test the clinical and cost-effectiveness of the optimised insole should it demonstrate to hold promise as an intervention.

This chapter starts with the context of the researcher's position. It will then present the consequences of the diabetic foot and its sequelae. An overview of the aetiology of DFU will be presented with an explanation as to how therapeutic footwear and insoles address the associated elevated plantar foot pressures to reduce the risk of DFU. Elevated plantar foot pressures are thought to be a significant contributory factor to DFU. This chapter also describes the current limitations of therapeutic footwear and insoles in the preventative management of DFU and justifies a novel optimised insole to reduce the risk of DFU. Lastly, the thesis structure is presented.

1.1 Researcher's background

This section provides a context to the researcher's position with regards to the research topic.

My journey as a podiatrist began 14 years ago when I started my podiatry undergraduate degree. After graduating and working for the NHS in various clinical settings, I completed a Masters in Clinical Podiatric Biomechanics. This experience gave me the skills and confidence to challenge the existing evidence base and treatment pathways to improve patient care.

My interest in techniques to offload the diabetic foot arose from working in clinics with people with neuropathic foot ulcers. Coming from a biomechanical perspective, I questioned the existing offloading methods and realised that there were opportunities to improve the treatment and reduce the risk of DFU. This perspective challenged the traditional prevention and treatment care pathways for diabetic foot ulcers, where the focus is predominantly on treating and managing the wound.

A desire to progress my knowledge and skills in applying biomechanical principles to the management of DFU prompted me to seek guidance from experts in the field. By introduction, I was fortunate to work closely with my Director of Studies, Dr Joanne Paton, who is one of the foremost experts in the UK in reducing the risk of DFU by footwear and insoles. I was invited to join the Balance Enhancement and Ulcer Prevention (BEUP) group, a multidisciplinary collaboration of academic and clinical members. The group aims to generate the evidence base and translate the results from published research to

influence and inform everyday clinical practice, focusing on the problems faced by people with diabetes and neuropathy. This association has inspired and motivated me to focus on offloading and reducing the risk of DFU for this vulnerable patient group.

1.2 The burden of diabetic foot ulceration

The World Health Organisation classifies DM as a group of metabolic disorders where hyperglycaemia is the 'principal component in the absence of treatment' (World Health Organisation, 2019). Estimates of the global prevalence of people with DM aged 20-79 years are 424.9 million, which is 8.8% of the world's population (International Diabetes Federation, 2020). By 2045, forecasts estimate prevalence to rise to 628.6 million or 9.9% of the world's population. In the UK, DM is estimated to affect 3.9 million people (9.7% of the adult population), with a predicted increase to five million by 2035 (Public Health England, 2015).

Globally, annual diabetic foot ulcer incidence rates are 6.3% of the DM population (Zhang *et al.*, 2017). A lifetime incidence of DFU for people with DM is estimated at between 19% and 34% (Armstrong, Boulton & Bus, 2017). A systematic review examining global DFU reported a prevalence of diabetic foot ulcers as 5.9% of the UK's DM population (Zhang *et al.*, 2017). Following ulcer healing, diabetic foot ulcer re-occurrence is likewise problematic. One systematic review scrutinised 21 studies to report global diabetic foot ulcer re-occurrence rates of 40% within one year after healing, 60% within three years, and 65% within five years (Armstrong, Boulton & Bus, 2017).

Diabetic foot ulceration precedes diabetes-related lower-limb amputations in 80% of cases (Hingorani *et al.*, 2016). An epidemiology study reported lower limb amputation rates of 7.5 per 100,000 for 21 member countries in the Organization for Economic Cooperation and Development between 2000 and 2015 (Carinci *et al.*, 2020). In England, based on data between 2015/16 to 2017/18, there are estimated to be more than 9,000 leg, toe or foot amputations every year for people with diabetes (PHE, 2019).

The presence of DFU is further associated with increased mortality rates. The risk of death at five years for those with a diabetic foot ulcer is reported as two and a half times higher than those without a diabetic foot ulcer (Walsh *et al.*, 2016). A meta-analysis comprising 11 observational studies reported relative risk as 2.45 (95% CI, 1.85–2.85) for mortality in people with DM who had DFU (Saluja *et al.*, 2020). In England, five-year mortality rates for first diabetic foot ulcer and first major amputations are 40% and 68% respectively (Kerr *et al.*, 2019). Likewise, a cohort study from Scotland reported crude two-year amputation-free survival rates in people as 81.6% in the active diabetic foot ulcer group and 76.1% in the healed diabetic foot ulcer group (Vadiveloo *et al.*, 2018).

These data demonstrates the considerable global burden of DM and DFU. They also provide alarming statistics that predict that this burden will progressively increase. Consequently, many strategies are utilised to reduce this burden. One such strategy is through the prevention of DFU.

1.3 Preventing diabetic foot ulceration

An effective way of reducing the costly burden of DFU and its consequences to patients and global health systems is by prevention. Estimates suggest reducing the prevalence of DFU by one-third in England would save more than £250,000 000 annually (Kerr *et al.*, 2019). One international report used the effect sizes of a range of different prevention strategies from controlled studies to hypothesise a 75-80% reduction in DFU recurrence when strategies are combined (Bus & van Netten, 2016).

National and International guidance advocates annual screening for people with DM to identify the level of risk of developing DFU (Bus *et al.*, 2020; NICE, 2015). Reiber et al.'s (1999) observational study based on 148 DPN patients from Manchester and Seattle used a Rothman model for causation approach to conclude a combination of peripheral neuropathy, deformity and trauma as the components present for two out of three diabetic foot ulcers (Reiber *et al.*, 1999). The authors additionally identified other component causes of peripheral vascular disease, callus and oedema. A history of DFU, elevated plantar pressures, previous amputation, poor glycaemic control, smoking and other microvascular complications have also been recognised as contributing to the pathway for neuropathic DFU (Boulton, 2013).

By targeting those individuals with the most significant risk factors of peripheral neuropathy and peripheral vascular disease using preventative strategies, the causal pathway to DFU could potentially be interrupted. The efficacy of preventive strategies in interrupting the causal pathway to DFU is diverse and dependent on many therapeutic and patient-related factors, including the timely

provision of treatment. The following section provides an appreciation of the causal pathway to DFU.

1.4 Pathway to diabetic foot ulceration

While the pathway to DFU is multi-factorial, there are two distinct categories of diabetic foot ulcer that represent different pathophysiological and clinical characteristics and require separate preventative pathways (Armstrong *et al.*, 2011), although frequently they overlap. One category is neuropathic DFU, where the ulceration is often found on the plantar surface of the foot (Edmonds & Foster, 2006). This type is characterised by peripheral neuropathy, elevated plantar foot pressures, deformity, and well-perfused tissue. Therapeutic footwear and insoles are considered an essential strategy in reducing the risk of neuropathic DFU (Bus *et al.*, 2020). The second category of DFU is neuro-ischaemic (Armstrong *et al.*, 2011; Armstrong, Lavery & Harkless, 1998), characterised by atherosclerosis of lower extremity arteries causing occlusive disease and neuropathy (Ho & Shanahan, 2016). Prevalence is estimated at 50% of people with ischaemic DFU (Hinchliffe *et al.*, 2016), although the prevention of this type of diabetic foot ulcer is beyond the scope of this thesis.

Cavanagh first described the events' sequence to developing neuropathic DFU (Cavanagh, Simoneau & Ulbrecht, 1993). Other authors have provided similar narratives, with Boulton in particular substantiating the concept (Armstrong *et al.*, 2013; Boulton, 2006; Boulton, 2020). The sequence to neuropathic DFU is initiated by the impact of diabetes and related complications. These complications can include the development of DPN, manifesting in sensory, autonomic, and motor changes to the foot. These changes potentially cause

elevated pressures under the foot, which incites tissue stress and provokes callus formation in response. If left untreated, the presence of excessive, repetitive application of tissue stress to the insensate foot results in DFU (Lazzarini *et al.*, 2019). As the focus of this work is on reducing the risk of neuropathic DFU, hereafter called DFU, the following section discusses this causal pathway of events in more detail. It describes how the progression of DM can cause a cascade of events that can lead to DFU.

1.4.1 Diabetes-related complications

The first event in the pathway to DFU is initiating the mechanisms by which DM can cause diabetic foot ulcer related complications. These mechanisms include the formation of advanced glycation end-products, increased oxidative stress, mitochondrial dysfunction, and activation of the polyol and hexosamine pathways (Giacco & Brownlee, 2010). Experimental studies have attributed these underlying mechanisms to inflammatory molecules' activation from persistent and extended periods of hyperglycaemia-mediated cellular damage (Ristikj-Stomnaroska, Risteska-Nejashmikj & Papazova, 2019). However, a Cochrane review reported that enhanced glucose control significantly prevented clinical neuropathy progression in only type-1 diabetes and not commonly in type-2 diabetes (Callaghan *et al.*, 2012). Components of metabolic syndrome may play a role in the onset and progression of diabetes-related complications (Sas *et al.*, 2016). A recent literature review investigating the onset and progression of diabetic complications reported that metabolic dysregulation should not only include hyperglycaemic but also alterations in systematic and local lipid metabolism (Eid *et al.*, 2019).

1.4.2 Diabetic peripheral neuropathy

The second event in the pathway to DFU is the onset and manifestation of complications, such as DPN. Complications are classified into macrovascular or microvascular disorders (Forbes & Cooper, 2013). Microvascular disorders include DPN and are a risk factor in the development of diabetic foot ulcers. A pooled analysis of 29 studies reports a global prevalence of DPN of 30% (95%

confidence interval, CI 25–34%) amongst the DM population, although DPN was assessed by sensory disruption only, as opposed to motor and autonomic changes (Sun *et al.*, 2020).

The pathogenesis of DPN is thought to be due to oxidative stress, which causes demyelination of the nerve fibres, the proliferation of Schwann cells, hypertrophy of the basal lamina, and axonal degeneration and damage (Vincent *et al.*, 2011). Within the lower extremity, DPN can affect all three nerve types; sensory, autonomic and motor (Gilbey, 2004; Schaper *et al.*, 2020). Each type of nerve dysfunction is contributory to the pathway of DFU.

Peripheral sensory neuropathy is characterised by a loss of the body's protective feedback mechanism in response to pain when injured (Boulton, 2010; Peltier, Goutman & Callaghan, 2014). Two prospective large-scale studies have reported the loss of foot sensation, as measured by a 5.07 monofilament, as most predictive of foot ulcer risk (Abbott *et al.*, 2002; Boyko *et al.*, 1999). The longest nerve fibres (A-delta) are affected first, and small-fibre (C-fibre) sensory neuropathy mainly affects pain and temperature sensations. A reduction or loss of pressure touch, vibration and proprioception sense, and subjective paraesthesia defines sensory neuropathy (Boulton, 1998; Boulton *et al.*, 2008).

Peripheral autonomic neuropathy is characterised by damage to the smaller peripheral sympathetic nerves, which results in decreased sudomotor responses (Tentolouris *et al.*, 2009). Clinical manifestations of autonomic neuropathy includes atrial venous shunting, reduced sweating, and ensuing anhydrosis of the skin. Atrial venous shunting is the impaired microvascular

thermoregulation. Decreased sweating is associated with the sweat glands' denervation to the skin (Gibbons *et al.*, 2009). One observational study reported dryness of the skin on the feet, as measured using a technique to assess moisture quantity at the foot's surface, was detected in 95% of subjects with diabetic foot ulcers (Tentolouris *et al.*, 2010). Peripheral autonomic neuropathy impairs the skin's ability to withstand the forces applied.

Peripheral motor neuropathy is linked with intrinsic foot muscle atrophy and weakness, distal migration of the fibro-fatty pad on the plantar aspect of the forefoot, limited joint mobility, and foot deformity. For example, experimental studies have found significantly reduced volume of intrinsic foot muscles for those with DPN than healthy non-diabetic controls and subjects with DM and no DPN (Andersen, Gjerstad & Jakobsen, 2004; Bus *et al.*, 2002). Two prospective studies have specifically investigated foot deformity as a causative factor for DFU. One under-powered study reported fixed hammer/claw toes (P=0.003) and hallux limitus (P=0.006) as significantly associated with DFU after adjusting for age, BMI and neuropathy (Ledoux *et al.*, 2005). The other study, similarly adjusted for neuropathy and other factors (age, BMI, insulin use), reported only hammer/claw toes and foot type (Charcot) were significantly linked to DFU (Cowley *et al.*, 2008).

In people with DPN, elevated plantar pressures are related to clinical features from motor neuropathy, such as limited joint range of motion (Fernando *et al.*, 1991; Zimny, Schatz & Pfohl, 2004), reduced ankle dorsiflexion (Mosteo, Spink & Chuter, 2018), deformity and bony prominences (Barn *et al.*, 2015), thickening of the Achilles tendon (Cronin *et al.*, 2010) and changes in gait

characteristics (Alam *et al.*, 2017). One study measured peak plantar pressures in people with DPN and claw or hammer deformity as 621kPa under the second and third metatarsal heads, compared to 363kPa in age-matched controls with DPN and no deformity (Bus *et al.*, 2005). Similarly, another experimental study reported a significant negative association ($r=-0.26$ to -0.61, $p < 0.0001$) between peak plantar pressure and plantar tissue thickness under all metatarsal heads for those with DPN and no history of diabetic foot ulcer (Abouaesha *et al.*, 2001). However, there has not been any evaluation of the relationship with severity of neuropathy and peak pressure magnitude.

1.4.3 Elevated plantar pressures

Following the development of DPN, the next event in the casual pathway to DFU is the elevation of plantar foot pressures. Boulton et al. (1983) first retrospectively compared barefoot feet pressures during walking using a microprocessor-controlled optical system. They reported ‘abnormally’ high pressures (above 1080 kPa) under the metatarsal heads for 51% of DPN participants, compared to 7% for healthy non-diabetic controls and 17% for DM without DPN controls (Boulton *et al.*, 1983). Since this time, several retrospective and prospective studies, typically with sample sizes of around 250 people with DM, have reported similar findings demonstrating that elevated barefoot plantar pressures (ranging between 588kPA to 1206 kPA) were significantly associated with a raised likelihood of DFU (Frykberg *et al.*, 1998; Pham *et al.*, 2000; Veves *et al.*, 1992). However, all of these studies were undertaken using barefoot analysis and did not report specific locations of elevated foot pressure.

More recently, a systematic review confirmed that overall barefoot mean peak pressure was higher in DPN, than diabetes controls without DPN and healthy non-diabetes controls (Fernando *et al.*, 2013). In this systematic review, a meta-analysis from three studies demonstrated greater mean plantar pressure in the forefoot of DPN patients at moderate effect levels compared to the healthy control group (standardised mean difference 0.55, 95% CI 0.20-0.90 p=0.002 I^2=0%) or DM group (standardised mean difference 0.51, 95% CI 0.24-0.78 p=0.001 I^2=10.1%) respectively. The review's limitations included the high level of heterogeneity between study designs, and participant foot risk severity levels and that all studies focused on barefoot analysis only.

Similar elevated plantar pressures in DPN have been found using in-shoe systems. A prospective study using a Fscan in-shoe system measured whole foot mean peak plantar pressure (MPPP) for DPN subjects wearing their “usual” footwear (Ledoux *et al.*, 2013). They reported higher MPPP (219 kPa ±16) for those with a history of diabetic foot ulcer compared to those without previous DFU (194 kPa ±2), although clinical significance was not established. Categorising the foot into regions, they highlighted that MPPP for the metatarsals was 383 kPa ±50 for participants with a history of DFU compared to 303 kPa ± 5 with no history of DFU.

Other studies have examined previous DFU sites and their relationship to elevated plantar pressure. All participants with DM and a history of DFU had abnormally high plantar pressures, above 1850 kPa, at the previous diabetic foot ulcer site in an early retrospective study (Boulton *et al.*, 1983). A large prospective study used univariate analysis to report that at sites of previous

DFU, an elevated barefoot peak pressure (> 200 kPa) was a significant independent risk factor of ulcer recurrence (Odds ratio = 1.38, (CI 95%1.05–1.81) p=0.023) (Waaijman *et al.*, 2013). However, in-shoe pressures were not significant (Odds ratio = 1.43 (CI 95% 0.89–2.32) p=0.142), and on-site data location was missing. Subsequently, the presence of elevated plantar foot pressures could progress to increased tissue stress in people with DPN.

1.4.4 Tissue stress - threshold for plantar pressure ulceration

The next event in the causal pathway to DFU is the increase in tissue stress prompted by elevated plantar pressures. However, despite elevated plantar pressures being a strong indicator of DFU, there is less convincing evidence of a pressure threshold magnitude at which DFU occurs. A case-controlled study involving 219 DPN participants with an active or previous healed diabetic foot ulcer compared to those without a history of foot ulceration reported a barefoot dynamic peak plantar pressure of 700 kPa to be 70% sensitive and 65% specific for diabetic foot ulcer development (Armstrong *et al.*, 1998). Another large-scale longitudinal study used a receiver operating characteristic (ROC) analysis to report a predictive barefoot pressure magnitude of 875kPa to be 63.5% sensitive and 46.3% specific for diabetic foot ulcer development (Lavery *et al.*, 2003).

Owings et al. (2009) used a Pedar in-shoe system to report a magnitude of 200kPa as a threshold for DFU (Owings *et al.*, 2009). The small cohort study followed 49 subjects with DPN and recently healed diabetic foot ulcer to report a mean in-shoe plantar pressure over 30 steps of 207kPa at sites of previous DFU, rounded down to 200kPa. Using a similar approach, Bus et al. (2011)

used a Pedar in-shoe system to quantify an absolute 200kPa threshold or a 25% reduction in mean peak pressure from baseline for optimisation of footwear and insoles. These thresholds were cited as arbitrarily significant, probably clinically relevant (Bus, Haspels & Busch-Westbroek, 2011).

These variations in threshold values for DFU between barefoot and in-shoe could be attributed to different methods, measurement systems, and wide spectrum of disease severity of DPN participants with diabetic foot ulcer pathology at different times of their care. Absolute comparison of barefoot and shod walking pressures is problematic due to methodological and measurement variances. A Swedish cohort study, for example, demonstrated that barefoot pressures were 36.5% higher than a Pedar in-shoe measurement system for DPN with previous DFU (Owings *et al.*, 2009). Furthermore, as peak pressure represents the vertical component only, other forces exerted parallel to the skin (shear or stress) would not be part of a threshold determination (Lott, Zou & Mueller, 2008). Patient behavioural factors such as the type and intensity of daily physical activity and adherence to prescribed treatment also influence any threshold for DFU (Bus, Waaijman & Nollet, 2012). A prospective large cohort study used multivariate analysis to report the combination of a low in-shoe peak pressure (below 200 kPa) and high adherence (greater than 80% of daylight hours) to footwear and insole usage as the predominant factors in diabetic foot ulcer reduction compared to standard therapeutic footwear (Waaijman *et al.*, 2013). They demonstrated a 50% diabetic foot ulcer risk reduction (Odds ratio =0.43 (95% CI, 0.20–0.94), p=0.033) with both components, but non-significant diabetic foot ulcer risk reduction (Odds ratio 0.80 (95% CI 0.44-1.47), p = 0.48) with low adherence in-shoe pressure footwear alone.

Recent guidance from the International Working Group for Diabetic Foot (IWGDF) suggests that for those with DM and a recently healed diabetic foot ulcer, a threshold of 200kPa or a reduction of 30% or greater in absolute peak pressure during walking should be used when producing therapeutic footwear and insoles (Bus *et al.*, 2020). Two studies demonstrated the beneficial effects of using these thresholds to inform the design of the therapeutic footwear and insoles when compared to current therapeutic footwear (Bus *et al.*, 2013; Ulbrecht *et al.*, 2014). There is no literature, however, to support a threshold of DFU for those with DM who have not had a previous diabetic foot ulcer. Similarly, there is no substantial evidence to validate that lowering peak plantar pressures reduces the risk of DFU. Yet, despite the absence of conclusive evidence to support a pressure threshold at which DFU occurs, the effect elevated plantar pressures are considered contributory to DFU.

1.4.5 Callus formation

The next event in the casual pathway to DFU is the presence of callus. The presence of callus on the foot usually indicates increased stresses on the skin due to the interface between the ground and the body during weight-bearing activities in standing and walking locomotion. Consequently, callus is classified as a risk factor for DFU and included in preventative screening guidance (NICE, 2015).

The pathogenesis of corns and callus is associated with the natural body's response to the altered mechanical stress (Grouios, 2004). Skin cells react to excessive pressure by increasing keratinocytes proliferation and forming hyperkeratosis, or callus (Arosi, Hiner & Rajbhandari, 2016). Experimental

studies have reported the altered mechanical properties and visco-elastic behaviour of plantar foot tissue in people with DM, which contribute to this process. One study found that plantar foot tissue has stiffer properties for people with DM than people without DM, altering the visco-elastic behaviour and making the tissue potentially more vulnerable to fatigue and failure (Gefen, 2003). In a similar approach, another study reported indentation tests on plantar heel pad and associated finite element modelling found Young's modulus of the skin of 5.86 MPa (±2.51) for people with DM compared to age-matched healthy controls of 7.05 MPa (±1.94) (Gwak *et al.*, 2020).

There is good evidence to link callus with sites of DFU (Reiber *et al.*, 1999). A small prospective study in the UK reported a relative risk of 11.0 of developing a diabetic foot ulcer under areas of callus (Murray *et al.*, 1996). However, callus is also formed in response to shear and compression forces (Marczak, Liberski & Migdalski, 2018). A cross-sectional observational study on participants with DPN used a novel measurement system to show that shear forces were contributory to sites of callus formation (Hamatani *et al.*, 2016). Unfortunately, the small sample size meant they could not differentiate the relative contributions of compression and shear to this callus formation. Nonetheless, the presence of callus indicates structural skin changes that could potentially develop into a diabetic foot ulcer.

1.4.6 Diabetic foot ulceration

The culmination of the pathway events is the damage to the skin and subcutaneous tissues at a cellular level that results in DFU. The International Working Group on the Diabetic Foot (IWGDF) describes a diabetic foot ulcer as;

‘A break of the skin of the foot that includes the epidermis minimally and part of the dermis in a person with currently or previously diagnosed diabetes mellitus and usually accompanied by neuropathy and/or peripheral arterial disease in the lower extremity” (van Netten *et al.*, 2020a).

The damage to the skin and tissues invokes a series of processes that end in cellular failure. A narrative literature review focussing predominantly on experimental studies described four processes by which a diabetic foot ulcer is thought to occur (Bader & Worsley, 2018). These processes are prolonged loading of the tissues that provokes induced ischaemia to cells, impaired interstitial and lymphatic flow, reperfusion injury and cell deformation. However, these processes are derived from studies focusing on pressure-induced ulceration in static loading conditions and not specific to DFU, and the relative contribution of each process to cellular failure and ultimately DFU is unclear.

Once a diabetic foot ulcer has manifested, there is an increased risk of incurring severe complications. The focus of management changes to healing, which brings considerable burdens to the patient and healthcare systems. Consequently, strategies to interrupt the causal pathway at an earlier stage are vital to reduce the risk of DFU. However, although the sequence of events described provides a logical pathway for causality, in reality, DFU is not as well-ordered and predictable. Patients rarely follow the sequential pathway, moving between event stages at different rates and frequently by-passing event stages altogether. Similarly, some patients who closely follow the causality pathway fail to incur a diabetic foot ulcer. This reinforces the notion that DFU is a complex interaction of multiple factors, some of which are not explained by the

predictable pathway of causality. Resultantly, introducing preventative strategies to interrupt the causal pathway may not be timely or appropriate for some to reduce the risk of DFU.

1.5 Therapeutic footwear and insoles

Although there are several methods of interrupting the causal pathway to neuropathic DFU, one specific preventative strategy is therapeutic footwear and insoles. National and international evidence-based guidance recommend using therapeutic footwear and insoles to reduce the risk of DFU and reduce plantar pressures (Bus *et al.*, 2020; NICE, 2015). Guidance in the UK recommends assessment for the provision of therapeutic footwear and insoles for any patient identified at moderate or high risk of DFU (NICE, 2015). It is recommended that assessment is undertaken by an orthotist or podiatrist and supported by providing two pairs of therapeutic shoes and insoles for people at risk of DFU, although national and regional variations exist. In my clinical area in Torbay, specialist therapeutic footwear and insoles cost between £100 and £420. In the UK, it was forecast that the cost of the provision of bespoke footwear and insoles to those at increased risk or high risk of DFU is £5.4 million (NICE, 2015).

One mechanism by which therapeutic footwear and insole is thought to act is by reducing elevated peak plantar foot pressures, particularly for those with DPN (Bus, Ulbrecht & Cavanagh, 2004). Several systematic reviews have provided an overview of the literature on the efficacy of therapeutic footwear and insoles in reducing DFU incidence or peak plantar pressures (Bus *et al.*, 2008; Bus *et al.*, 2016; Heuch & Streak Gomersall, 2016; Paton *et al.*, 2011; van Netten *et*

al., 2016). Paton's review included five studies but reported findings from four, suggesting that insoles appear effective in reducing plantar pressures in DPN and reducing the incidence of DFU (Paton *et al.*, 2011). However, the reported studies' methodological quality was low and there was no endorsement regarding the type and specification of insole provided. Heuch's review focused on preventing first diabetic foot ulcer and included three studies of low-quality evidence (Heuch & Streak Gomersall, 2016). They concluded that the use of therapeutic footwear with customized or prefabricated insoles might provide some reduction in plantar pressure. They inferred a causal link to the prevention of a primary diabetic foot ulcer. Van Netten's review complemented these findings that focused on the prevention of DFU. He concluded few controlled studies, of generally low to moderate quality, were identified on the prevention of a first diabetic foot ulcer, although multiple RCT's with low risk of bias were identified for the prevention of recurrent plantar DFU (van Netten *et al.*, 2016). This was a similar finding to Bus's latter work, which identified 20 studies of varying design and risk of bias. Both reviews concluded there is increased

efficacy of therapeutic footwear and insoles that display plantar pressure relief, and are worn by the patient, in the prevention of plantar DFU recurrence (Bus *et al.*, 2016).

A more recent systematic review provides a contradictory viewpoint to the evidence to support the use of therapeutic footwear and insoles in the prevention of DFU (Crawford *et al.*, 2020). Initially, they pooled the effects of six studies of variable quality to report a beneficial effect of therapeutic footwear and insoles in reducing DFU (RR 0.53 (95% CI, 0.33-0.85). However, when

excluding those studies with participants without a history of diabetic foot ulcers, they found no statistical difference in the number of re-occurring diabetic foot ulcers between the therapeutic footwear and control groups (RR (0.71 (95% CI, 0.47-1.06). Consequently, the ambiguity in the efficacy of therapeutic footwear and insoles in reducing the risk of DFU, for those with and without previous diabetic foot ulcers, and the inadequate reporting of the design features, provide challenges to clinical practice implementation.

1.6 The challenges of using therapeutic footwear and insoles

Several challenges impact negatively upon the implementation of therapeutic footwear and insoles to reduce the risk of DFU. These challenges are: 1) Variability in pressure-reduction; 2) Evaluation of the therapeutic effect; 3) Variability of the design process; 4) Clinicians role in the design and provision; 5) Delays to provision.

1.6.1 Variability in pressure-reduction

There is substantial variation in the efficacy of therapeutic footwear and insole interventions, with sizeable inter-participant variation in pressure reduction reported for people with DPN. For example, one RCT noted no statistical difference in kinematic outcomes between prefabricated off-the-shelf insoles and custom-made insoles (CMI) informed by participants' foot mechanics (Paton *et al.*, 2012). However, in both intervention groups, the effect of the insole varied considerably from person to person. Similarly, Bus et al. (2004) reported a significant overall reduction in peak-pressure (PP) with a CMI across all 20 participants but a variable effect at an individual level (Bus, Ulbrecht &

Cavanagh, 2004). The authors described seven out of the 21 insoles were not successful, designated as a significant reduction in PP and FTI, in offloading the regions of interest compared with a simple flat insole.

1.6.2 Evaluation of the therapeutic effect

The clinical evaluation of the effect of any therapeutic footwear and insole intervention in people with DPN is limited and complex. Patient feedback, for instance, is inadequate since sensory impairment means that participants cannot determine whether the therapeutic footwear and insole are comfortable or not. In clinical practice, therefore, therapeutic footwear and insole design and plantar pressure evaluation are typically undertaken using a 'trial-and-error approach' (Waaijman *et al.*, 2012). This reliance on observational monitoring of foot health means that clinicians adopt a strategy of treating clinical symptoms (an observed deterioration in foot health) rather than initiating a preventive strategy to reduce risk factors such as high plantar pressures.

1.6.3 Variability of the design process

The absence of a standardised process for the design and provision of therapeutic footwear and insole to reduce the risk of DFU provides uncertainty for implementation. The over-arching mechanism by which therapeutic footwear and insoles reduce the risk of DFU is by relieving, reducing, or redistributing elevated foot plantar pressures (Pendsey, 2010). However, the mechanisms by which different design features act are often unexplained (Bus, Ulbrecht & Cavanagh, 2004; Waaijman *et al.*, 2012). There are frequently insufficient details of therapeutic footwear and insole specifications disclosed in studies to enable standardisation in clinical practice (Paton *et al.*, 2011). This lack of

detail, together with the varying methodological quality of existing studies, makes it difficult to translate these findings into clinical decision making

1.6.4 Clinicians role in the design and provision

The clinician's role in the design and provision of therapeutic footwear and insoles to reduce the risk of DFU is also variable. Analysis from a large-scale postal survey in the UK reported a wide range of therapeutic footwear and insoles are provided by different health professions in different ways (Nester *et al.*, 2018). A web-based, international, cross-sectional survey of prescribers of insoles found that UK respondents were more likely to prescribe prefabricated insoles for people with DM without DPN and CMI's for those with DPN (Chapman *et al.*, 2018). One qualitative study used a focus group methodology and thematic framework analysis to cite the absence of a singular algorithm as an influencing factor for the variation in insole prescriptions (Williams *et al.*, 2016). Other themes included resistance to change current practice and barriers to using technology in prescribing insoles for NHS podiatrists and orthotists in the UK. An additional barrier to providing an appropriate prescription for therapeutic footwear and insoles may be that some practitioners are not trained to specify appropriate footwear interventions in preventing DFU (Cavanagh & Bus, 2010).

1.6.5 Delays to provision

There are frequently detrimental delays in people receiving the necessary therapeutic footwear and insoles due to manufacturing lags, clinical provision, and procurement waits. One systematic review based on 32 diabetic foot ulcer studies reported that delays in treatment provision are associated with

detrimental outcomes for patients (Nickinson *et al.*, 2020). Offsite commercial providers usually undertake the manufacture of therapeutic footwear and insoles over several weeks. A prospective analysis of a therapeutic footwear service in the UK reported the average time from the first appointment to shoe fitting was nine weeks (range 3-20 weeks) (Dhatariya, Panter & Gooday, 2011). Similarly, a clinical audit undertaken in 2016 within my workplace at Torbay indicated waits of up to 18 weeks for insole provision and 24 weeks for therapeutic footwear provision from the first assessment (unpublished).

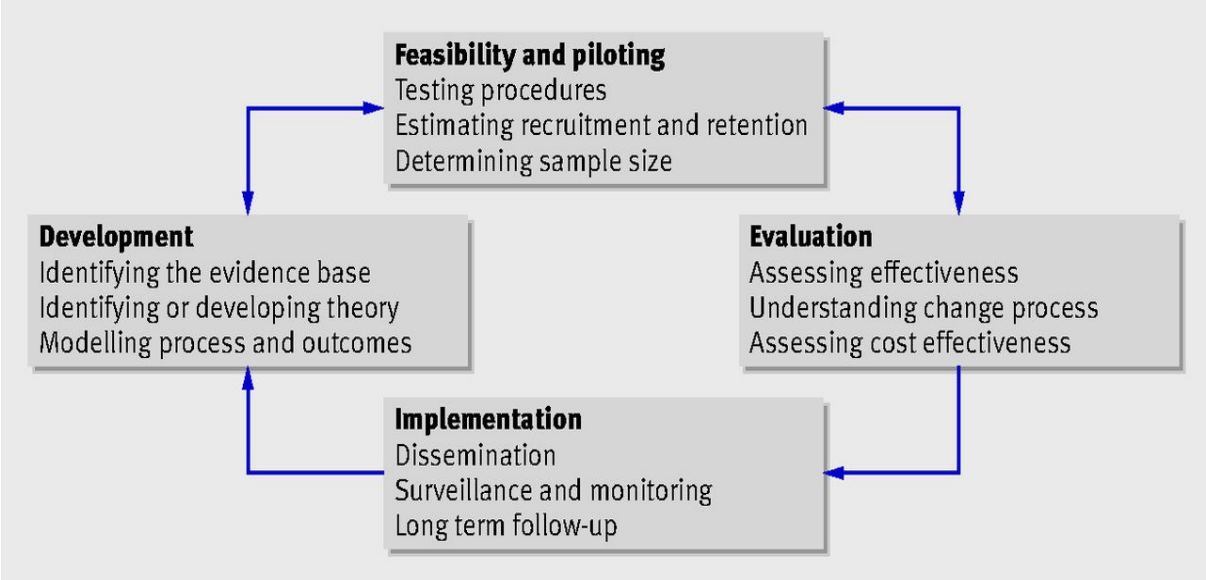
1.7 A potential solution: the optimised insole

One potential solution to the challenges posed by therapeutic footwear and insoles in reducing the risk of DFU is the 'optimised insole.' The optimised insole proposed to address the problems highlighted in reducing the risk of DFU and reducing elevated plantar pressures. The optimised insole used in-shoe plantar analysis to gather real-time pressure mapping to inform its design and optimisation, guided by an 'optimised insole algorithm.' The use of real-time pressure mapping is relevant and cutting edge and is not used in current practice, although it has been used in research projects. The insoles were appropriate for chairside delivery. They were made from commercially available materials and fitted within an off-the-shelf house shoe and issued to the patient within a single outpatient visit, reducing timely issuing delays. The optimised insole provided an objective and standardised approach, using quantitative evaluation to design, modify and monitor the insole's performance in reducing peak plantar pressures. At the same time, it enabled a person-by-person optimisation rather than a generic prescription.

1.8 Development of the optimised insole

The UK Medical Research Council (MRC) conceptual framework for developing and evaluating complex interventions (Craig *et al.*, 2008) (hereon referred to as the MRC Framework) guided the development of the optimised insole. It provides a phased and structured approach to complex intervention design, development, testing, evaluation and implementation, thereby enabling the systematic accumulation of evidence to support the development and testing of the intervention (Michie *et al.*, 2012). Such an approach improves the quality and generalisability of complex interventions in health care (Campbell *et al.*, 2000).

The MRC framework encompasses four stages of develop-test-evaluate-implement (Figure1.1). Develop consists of identifying the evidence base, developing the theory, and then modelling the process and outcome for developing the complex intervention. Test consists of feasibility or piloting of the complex intervention, whereby procedures are tested, estimates of recruitment and retention occur, and the sample size is determined. This step is where researchers aim to address key uncertainties with the complex intervention before proceeding to the next phase (Craig *et al.*, 2008). Evaluate consists of assessing the effectiveness and cost-effectiveness of the complex intervention while understanding the change process, and implement refers to dissemination, surveillance, monitoring and long-term follow-up to ensure any recognised effect are maintained. Pragmatically, researchers often move iteratively between stages rather than following a linear or cyclical sequence (Craig *et al.*, 2008).



(Figure used by kind permission of the Medical Research Council, as part of UK Research and Innovation, reprinted with permission license number: 4990170877197)

Figure 1.1 Medical Research Council's framework for developing and evaluating complex interventions

In response to limitations, this MRC framework has undergone several iterations since its inception. Originally planned as a discussion document, concerns were voiced over its focus on evaluating complex interventions in randomised trials related to drug intervention, with no mention of process evaluation (Campbell *et al.*, 2000). Some authors considered the definition of the complexity of interventions as too narrow (Shiell, Hawe & Gold, 2008) and that pragmatically, the context contains a range of dynamic influences rather than a static process (Wells *et al.*, 2012). In response to these concerns, the framework was expanded to include planned development, feasibility and pilot, evaluation, and implementation (Craig *et al.*, 2008). More recently, the provision of a process evaluation framework to include behavioural models (Moore *et al.*, 2015) and comprehensive guidance (Craig *et al.*, 2020; Skivington *et al.*, 2018)

has enhanced the framework. Regrettably, these later expansions were not accessible to inform this study. Consequently, this research study is based on the 2008 version of the framework (Craig *et al.*, 2008).

This research study sits in the MRC conceptual framework for developing and evaluating complex interventions and reports the 'develop' and 'test' phases. Complex interventions are considered 'interventions with several interacting components that impact the length and complexity of the causal chain from intervention to outcome and the influence of features of the local context' (Craig *et al.*, 2008). The complex mechanisms involved in the aetiology and prevention of DFU have been frequently cited (Jeffcoate *et al.*, 2018). The MRC framework is, therefore, appropriate to examine this complex clinical intervention.

1.9 Structure of the thesis

This chapter has provided an introduction and background to the enormous burden that is concomitant with DFU. It has presented a causal pathway to DFU for those with DPN and highlighted the role of therapeutic footwear and insoles as a preventative strategy. Acknowledged are the many challenges that exist in providing therapeutic footwear and insoles which reduce the risk of DFU. Resultantly, the concept of the 'optimised insole' as a potential solution to these challenges has been established.

Chapters two and three will present the development of the optimised insole as a potential strategy to reduce the risk of DFU. Chapter two presents a novel systematic review and meta-analyses that is the first to summarise the best available evidence of therapeutic footwear and insole design features for offloading the diabetic foot. Chapter three presents the development framework

for the optimised insole and the theoretical construct underpinning the use of real-time pressure mapping to inform the design of the optimised insole. This culminates in the optimised insole algorithm, which demonstrates novel thought in its application to reduce the risk of DFU in people with DPN. Chapter four describes and justifies the feasibility study design to test the acceptability of procedures to evaluate the optimised insole intervention. Chapter five presents the quantitative results, and Chapter six describes the qualitative findings from the feasibility study. Chapter seven provides a discussion of the results and findings, with Chapter eight formulating recommendations and conclusions for future research.

Chapter 2 Systematic literature review

In the previous chapter, the potential of the optimised insole as a complex intervention to reduce the risk of DFU was established. The first step of the MRC's framework when developing and evaluating a complex intervention involved identifying the evidence base.

Previous systematic reviews have evidenced the effectiveness of insoles and footwear in reducing plantar foot pressure for people with DPN and preventing DFU (Bus *et al.*, 2008; Bus *et al.*, 2016; Heuch & Streak Gomersall, 2016; Paton *et al.*, 2011; van Netten *et al.*, 2016). However, each failed to identify and report the effectiveness of particular design features for insole and footwear. Even when footwear and insole interventions and their components are clearly described and evaluated, the processes that have shaped their concept, design and use are rarely reported. This gap in the evidence provides uncertainty for the clinical application of particular footwear and insole features for reducing the risk of DFU. Consequently, there are variations in the design process and clinicians' knowledge and understanding of footwear and insole provision for this purpose.

In this chapter, a systematic literature review based on a published protocol (Collings *et al.*, 2017), provides a detailed overview of the existing evidence to identify the best footwear and insole design features for offloading the plantar surface of the foot to prevent DFU in people with DPN. This systematic review is novel as it is the first review to consider the design features used to offload the foot in people with DPN. The results of this review informed the development of the optimised insole algorithm to standardise the clinical design

of therapeutic insoles and footwear to reduce the risk of DFU in people with diabetes and DPN. The systematic review commenced in May 2016 with preliminary findings informing the development of the optimised insole algorithm. Subsequent interruptions (change of Joanna Briggs Institute software system, feasibility trial set-up and management) caused the delay in the publication of the systematic review until 2020 (Collings *et al.*, 2020). Updated literature searches ensured the findings were contemporary before the accepted submission.

This systematic review highlighted the difficulty in differentiating insole and footwear features in offloading the neuropathic diabetic foot. However, its results demonstrated that arch profiles, metatarsal additions, and apertures effectively reduce plantar pressure. The use of pressure analysis to enhance the design of footwear and insoles, particularly through modification, was recommended.

The systematic review presented in this chapter is the accepted word version published in Endocrinology, Diabetes, and Metabolism (Collings *et al.*, 2020). Consistent with the accepted format for the journal, references are cited in Vancouver style, which enhances its readability. Resultantly, the full list of references for this paper are included at the end of the chapter, followed by the hyperlinks to the electronic supplementary material.

The bibliographical details of the work, a description of the work and an estimated percentage of contribution (%) of each author are as follows: Collings, R. (85%), Freeman, J. (5%) Latour, J.M. (5%), Paton, J. (5%). The percentages of contribution were agreed among all authors.

Title: Footwear and insole design features for offloading the diabetic at risk foot - A Systematic Review and Meta-Analyses

Endocrinology Diabetes Metabolism. 2020;00:e00132.
https://doi.org/10.1002/edm2.132

Date accepted: 14th March 2020

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Keywords - diabetic foot; prevention; offloading; footwear; insoles; systematic review

2.1 Abstract

The aim of this systematic review is to identify the best footwear and insole design features for offloading the plantar surface of the foot to prevent foot ulceration in people with diabetic peripheral neuropathy. We searched multiple databases for published and unpublished studies reporting offloading footwear and insoles for people with diabetic neuropathy and non-ulcerated feet. Primary outcome was foot ulcer incidence; other outcome measures considered were any standardised kinetic or kinematic measure indicating loading or offloading the plantar foot. Fifty-four studies, including randomized controlled studies, cohort studies, case-series, and a case-controlled and cross-sectional study were included. Three meta-analyses were conducted and random effects modelling found peak plantar pressure reduction of arch profile (37 kPa (MD, -37.5; 95% CI, -72.29 to -3.61; $p < 0.03$), metatarsal addition (35.96 kPa (MD, -35.96; 95% CI, -57.33 to -14.60; $p < 0.001$) and pressure informed design 75.4kPa (MD, -75.4kPa; 95% CI, -127.4kPa to -23.44 kPa; $p < 0.004$).The remaining data were presented in a narrative form due to heterogeneity. This review highlights the difficulty in differentiating the effect of different insole and footwear features in offloading the neuropathic diabetic foot. However, arch profiles, metatarsal additions and apertures are effective in reducing plantar pressure. The use of pressure analysis to enhance the effectiveness of the design of footwear and insoles, particularly through modification, is recommended.

2.2 Introduction

Foot ulceration is amongst the most serious complications of diabetes mellitus [1]. It is expected that 19-34% of people with diabetes will develop a foot ulcer at some point [2]. Foot ulceration is known to precede 80% of all diabetic lower limb amputations [3,4]. A longitudinal study of a diabetic community reported new ulcer incidence as an estimated 2% annually [5] whilst other studies have noted ulcer re-occurrence rates of 30-40% in the first year after an ulcer episode [2,6,7]. Prevention of foot ulceration occurrence and reoccurrence are now recognised as key strategies in reducing the concomitant burden to patients with diabetes and the healthcare system [8].

The cause of diabetic foot ulceration is multifactorial [9]. However, reducing high plantar loads or foot pressures is one mechanism by which foot ulceration may be prevented [10]. Elevated dynamic plantar pressures during locomotion contribute to the development of plantar diabetic foot ulcers when in the presence of neuropathy [11, 12]. Guidelines recommended that people with diabetes wear appropriate 'diabetic footwear' designed to reduce repetitive stresses at all times [13]. Systematic reviews have demonstrated the effectiveness of footwear and insoles in offloading the plantar load under the foot and preventing ulceration [14-18]. However, these have not identified the best insole design or feature and footwear specification or modification for use when reducing plantar load for foot ulcer prevention in people with diabetes and neuropathy.

Therefore the purpose of this systematic literature review is to identify the best footwear and insole design features for offloading the plantar surface of the foot

to prevent foot ulceration in people with diabetes. It is anticipated that this information will inform a standardised protocol for the clinical design of therapeutic insoles and footwear to offload the foot and reduce ulcer risk in people with diabetes and neuropathy.

More specifically, the objectives are to identify the key design features with regard to:

- profile/shape of the insole, shoe upper and shoe outsole
- material type and properties of the insole and shoe outsole
- modifications made to the insole and shoe outsole
- fabrication techniques used for the insole and shoe

2.3 Methods

This systematic review was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidance [19]. The systematic review was prospectively registered on the PROSPERO database for systematic reviews (CRD42017072816).

The population of interest was adults over 18 years of age with type 1 or 2 diabetes mellitus and peripheral neuropathy. The primary outcome was foot ulcer incidence; other outcome measures considered were any standardised kinetic or kinematic measure indicating loading or offloading the plantar foot (such as plantar pressure, pressure-time integral, total contact area, dynamic measures of centre of pressure trajectory or velocity) and any standardised clinical measure indicating loading/offloading of the plantar foot (such as

callus/lesion reduction). Side effects/adverse events as a result of the design features were additional outcomes of interest. We excluded studies on people with active ulceration, major amputation of the foot or Charcot arthropathy because we considered that the unique patho-mechanics and gross deformity associated with the severity of these conditions would unduly influence the design features of the footwear and insoles.

This review included both experimental and epidemiological study designs including randomised controlled trials, non-randomised controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies and analytical cross-sectional studies. Studies were included if they made one of the following comparisons: Footwear and/or insole design feature compared to another therapeutic footwear and/or insole design feature; footwear and/or insole design feature compared to no intervention. Qualitative studies, case reports and systematic reviews were excluded.

The initial literature search was performed on 27 July 2016 by one researcher (RC) and covered publications in English and was not restricted by date. The search was updated on 27 December 2017 and 30th October 2019. The following databases were searched: Excerpta Medica Database (EMBASE) via Ovid, Medline and Cochrane Database of Systematic Reviews, AMED (EBSCO), Cumulative Index to Nursing and Allied Health Literature (CINAHL), MEDLINE, Joanna Briggs Institute Database of Systematic Reviews, and PROSPERO. A search for unpublished studies was undertaken in EThOS, Pearl, Web of Science, Google Scholar, SIGLE. The search strings were prepared with the help of an evidence synthesis specialist. An example of the

search from one of the databases is provided in electronic supplementary material 1. Title and abstract of all papers retrieved by the literature search were screened independently by two researchers (RC and JP) to determine whether the paper met the inclusion criteria with disagreements resolved by discussion. Full text articles were then retrieved and further screened by two researchers (RC and JP) independently for inclusion in the review. In addition, a hand search was undertaken using the references from journal articles.

2.4 Results

The initial electronic search generated 7384 articles of which 2094 were duplicates (Figure 2.1). In the screening phase, 4750 were excluded based on their title and a further 466 excluded on title and abstract leaving 74 articles for full text assessment. We excluded 28 of these articles based on irrelevant study population (n=12), irrelevant study design (n=4), irrelevant outcome/ intervention (n=12) leaving 46 [20-65] included in the final review. As the initial search was undertaken in July 2016, updated searches were performed in December 2017 yielding 6918 articles, from which an additional three studies [66-68] were included and November 2019 yielding 7821 articles from which a further five studies [69-73] were included.

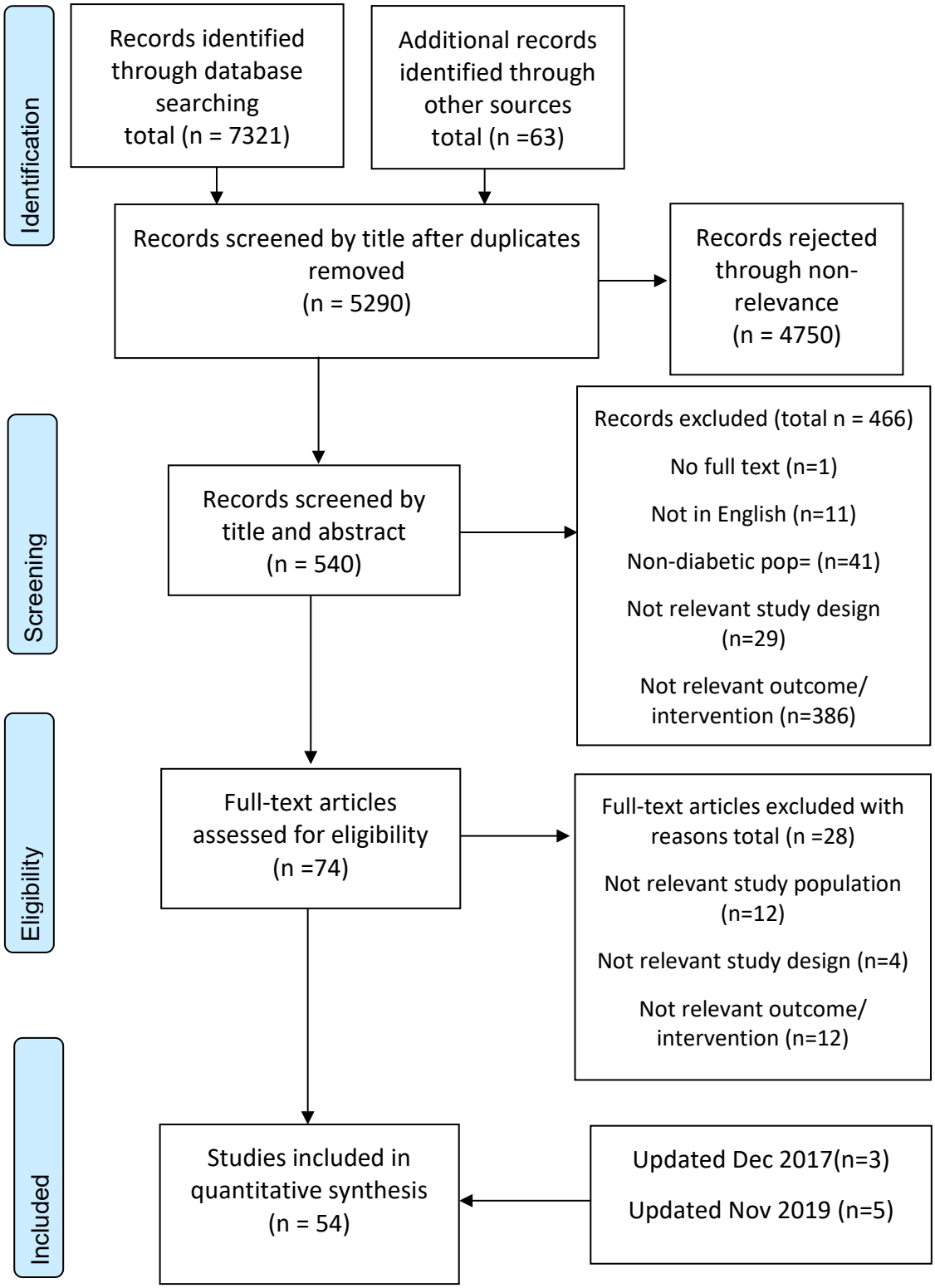


Figure 2.1 Flow diagram of study selection in July 2016 and updated in December 2017 and November 2019

2.4.1 Data extraction

Data extraction of included studies was conducted using JBI Meta-Analysis of Statistics: Assessment and Review Instrument (JBI-MAStARI)[74]. In this phase, the general and contextual data was extracted in relation to the population, study design, interventions (features, design, modifications and materials of footwear and insoles) and outcomes. In addition, relevant information was extracted in the results section. Data extraction was carried out by (RC) and checked by the second reviewer (JP).

2.4.2 Data analysis and synthesis

In this review, we summarised study findings quantitatively and pooled study effects in a meta-analysis when appropriate using JBI MAStARI [74]. Meta-analysis was performed using random-effects models for continuous variables, calculating mean differences using the inverse variance method. Meta-analysis was based on changes from baseline for peak pressure when the mean and SD were reported where any footwear or insole design feature, modification, material or method could be distinguished. Means and SD's of data was required to be included in the meta-analysis; we contacted four corresponding authors to request this data when not included in the article; two authors did not respond and one no longer had access to the data.

For all estimates, we computed the 95% confidence intervals (CI's). We quantified statistical heterogeneity using the I-Squared statistic (I2) and considered heterogeneity as low (<25%), moderate (>25% to 50%), or high (>50%) 75, although we did not pre-specify any degree of heterogeneity that would preclude meta-analytic pooling.

2.4.3 Assessment of study quality

Two reviewers (RC and JP) independently assessed the methodological quality of the studies using the relevant JBI critical appraisal tools [76]. Disagreements were resolved through consensus meeting. A study was considered low risk of bias if all criteria was included. Summaries of the appraisal of study quality are included in electronic supplementary material 2. All studies had some form of bias with standards of reporting variable across studies and by study design. From the quality assessment of the randomised controlled trials (RCT's, all of the RCT studies had some form of bias (mean percentage of 'yes' scores = 65% ± SD 29%). All RCT studies reported inclusion criteria of participants, p values and participants lost to follow up. The most frequent omissions related to the blinding of the assessor and participants, concealing of treatment allocation and outcomes measurement. Within all of the cohort studies, some form of bias existed (mean percentage of 'yes' scores = 56% (± s.d. 31%). The most frequent omissions related to confounding factors, short follow up periods and incomplete follow up. Within the case-controlled studies mean percentage of 'yes' scores = 70% (± s.d. 0%). Omissions related to confounding factors, lack of sample size justification and different criteria used for the identification of cases and controls. For the case series study, percentage of 'yes' scores = 60%. Omissions related to inclusion criteria, reporting of demographics and participants' characteristics. For the non-randomised cross over study, percentage of 'yes' scores = 75% with omissions relating to confounding factors and selection bias.

2.4.4 Characteristics of included studies

Study characteristics are reported in Table 2.1. Fifty-four studies met the inclusion criteria. Study designs included: n=13 RCT's [23,25,31,38,42,49,55,56,61,62,70,73,77], n=37 cohort studies [20-22,24,26-30,32-37,39-41,43,45,47-49,51-54,57-60,64,66-68,71,72], n=2 case control studies [44,63], n=1 non-intervention case series study [46] and n=1 non-randomised cross sectional over trial [65]. Four authors reported results of the same study in different papers [21,22,39,40,45,47,49,50] and therefore results from these studies were described, but only one set of each results was used within any meta-analysis. Studies were published between 1975 and 2019, undertaken in US (n=17) [20,24,33,35,37,42,45-48,51,54,55,58,59,62,65], UK (n=10) [23,30,32,49,50,67,68,71,73,77], Netherlands (n=7) [21,22,26,27,36,52,64], Germany (n=4)[28,29,44,57], Italy (n=2)[56,61], Australia (n=3)[25,31,53], Taiwan (n=3) [39,40,43], Spain (n=2) [34,70], Thailand (n=2)[66,72], Austria (n=1)[41], Sweden (n=1)[38], Hong Kong (n=1)[60], India (n=1)[63]. The number of participants recruited to treatment groups ranged from seven to 298. Twenty-seven studies (50%) recruited participants with diabetes mellitus and peripheral neuropathy whilst 19 studies (35%) recruited participants with diabetes mellitus, peripheral neuropathy and history of foot ulceration; a further two studies recruited participants with diabetes mellitus and peripheral arterial disease; three studies recruited participants with diabetes mellitus and classified at high risk of foot ulceration; two studies recruited participants with diabetes mellitus only; two studies recruited participants with diabetes mellitus, peripheral neuropathy and high forefoot pressures; one study recruited participants with diabetes mellitus, peripheral neuropathy and foot deformity; one study recruited participants with diabetes mellitus and foot callus; one study recruited participants with diabetes

mellitus and taking insulin; one study recruited participants with diabetes mellitus and classified at low risk of foot ulceration. Follow up time periods ranged from no follow up to five years.

Table 2.1 Characteristics of included studies

Author/year	Study setting	Study design	Participants	Age / years (s.d.)	Gender Male: Female	Comparator	Follow up period	Outcomes
(Abbott *et al.*, 2019)[77]	UK	RCT	N=58 DPN with history of previous foot ulceration	Control group 67.1 (9.6); intervention group 59.1 (8.5)	51:7	No plantar pressure feedback provided	18 months	68% ulcer free in control group and 78% in intervention group
(Albert & Rinoie, 1994)[20]	US	Cohort study	n=8 DPN	67 (10.1)	Unknown	Without orthotic	3 months	PPP↓ 30-40% under 1st MTPJ & medial heel. 5-10% ↑Total contact area
(Arts *et al.*, 2015)[21]	Netherlands	Cohort study	n=85 DPN, recently healed plantar foot ulcer	62.6 (10.2)	70:15	Pre-modification	15 months	PPP↓23% at target location; PPP↓ 13.5-24% by adding metatarsal bar or pad with replacement of top-cover
(Arts *et al.*, 2012)[22]	Netherlands	Cohort study	n=171 DPN with recently healed ulcer	62.8 (10.2)	140:31	Barefoot	Unknown	PPP↓ 50-76% (deformed feet), 14-66% (non-deformed feet) 85% (previous ulcer location). 61% Successfully offloading below 200kPa & 62% at previous ulcer site.

Table 2.1 (continued) Characteristics of included studies

(Barnett, 2002)[23]	UK	RCT	n=102 DM	Orthoses group=56 (20-75) Cleron group 62 (18-75)	68:35	3mm Cleron flat insoles	6 months	With orthoses: (22% MPPP↓, 16% Pressure time integral↓ & 11%↑mean Contact area); With insoles (16% ↓MPPP, 10% Pressure time integral↓ & 2%↑ mean Contact area)
(Birke, Foto & Pfiefer, 1999)[24]	US	Cohort study	n=19 DM with history of foot ulceration	60.2 (9.8)	11:8	Patients own CMI & footwear & no orthosis	n/a	Mean PPP↓55% (wearing own CMI & shoe vs without insoles). mean PPP↓ 36-39% (standard shoe wearing ¼ inch medium hardness poron vs shoe without orthoses)
(Burns *et al.*, 2009)[25]	Australia	RCT	n=61 DM with PAD & MSK pain.	Custom group = 67.6(8.4) Sham group =65.4 (10.3)	37:24	Sham insole	8 weeks	Whole foot Mean PPP↓(18% CMI vs 8% sham); Rearfoot Mean PP↓(27% CMI vs 4% sham); Midfoot Mean PPP↓ (7% CMI vs 4% sham); Forefoot mean PPP↓(16% CMI vs 10% sham)
(Bus, Ulbrecht & Cavanagh, 2004)[27]	Netherlands	Cohort study	n=20 DPN with foot deformity	64.4 (11.2)	13:7	0.95cm PPT flat insole	n/a	PPP↓16% & Force time integral↓ with CMI vs 8% with flat insole at 1st MTPJ

Table 2.1 (continued) Characteristics of included studies

(Bus, Haspels & Busch-Westbroek, 2011)[26]	Netherlands	Cohort study	n=23 DPN	59.1 (12.6)	17:6	Pre & post modification		All 35 ROI's successfully optimised with average of 30% ↓ PPP
(Busch & Chantelau, 2003)[28]	Germany	Cohort study	n=92 DPN with history of healed ulceration	64	49:43	Without footwear provided	19 months (shoes) vs 5 months (without shoes)	45% Absolute ulcer risk reduction for with shoes in 1st year
(Chantelau, Kushner & Spraul, 1990)[29]	Germany	Cohort study	n=50 DPN	59 (12)	31:19	With therapeutic footwear	25 months	Foot lesions =78% pre intervention vs 41% post
(Chapman *et al.*, 2013)[30]	UK/ Germany	Cohort	n=24 healthy & n=24 people with DM	57 (8)	31:17	Control	n/a	Variations in apex angle: 14% maximum pressure↓(1st MTPJ) & pressure↑(heel) vs control. For variations in apex position: 39% maximum pressure↓ at 2-4MTPJ vs control. As rocker angle ↑ there was ↓ in PP (5th MTPJ) & ↑ in pressure (hallux).

Table 2.1 (continued) Characteristics of included studies

(Colagiuri *et al.*, 1995)[31]	Australia	RCT	n=20 DM & with callus	Orthotic group 63(10); podiatry group 69(6)	5:15	Traditional treatment of callus	12 months	Callus grade improved in 16/22 callus sites (orthotic treatment group); remained unchanged in 23/30 & 7 deteriorated (traditional treatment group).
(Cumming & Bayliff, 2011)[32]	UK	Cohort study	n=20 DM with vascular or neurological impairment	68	unknown	No insole	1 week	Mean total pressure: wearing insole (0.180kg/cm^2/s), no insoles (0.210kg/cm^2/s). Mean pressure redistribution Poron 96 (0.198kg/cm^2/s), Poron 4400 (0.211 kg/cm^2/s); total difference (0.013 kg/cm^2/s).
(Donaghue *et al.*, 1996)[33]	US	Cohort study	n=50 DM at high risk of foot ulceration	57.6 (34-78)	32:18	Old footwear	3 & 6 months	Peak force at baseline: socks only (6.15 kg cm^{-2}), own socks & shoes (4.46 kg cm^{-2}), new socks & shoes (3.98 kg cm^{-2}). Mean PPP at 3 months with new socks & shoes (4.13 kg cm^{-2}) & 6 months (4.24 kg cm^{-2})

Table 2.1 (continued) Characteristics of included studies

(Fernandez *et al.*, 2013)[34]	Spain	Cohort study	n=117 DM with high risk foot factors & DFU history	Unknown	93:24	2 years pre intervention	Follow up 24 months	Pre orthotic 147 ulcerations; post orthotic 22 ulcerations. Mean PPP with orthotic treatment ↓ 85.2kPa (left foot) & ↓87.6kPa (right foot)
(Frykberg *et al.*, 2002)[35]	US	Cohort study	n=25 subjects (10DM, 15 healthy) with various foot shapes	37 (13.5)	13:12	Patients own tennis or oxford shoe	n/a	For DM subjects Mean PPP with: own shoe (4.46 kg/cm²), Surgical boot (4.89kg/cm²), Surgical boot & rocker insole (2.50kg/cm²). For non-diabetic subjects Mean PPP with: own shoe(2.07 kg/cm²), surgical boot (2.13kg/cm²), Surgical boot & rocker insole (1.13kg/cm²)
(Guldemond *et al.*, 2007)[36]	Netherlands	Cohort study	n=17 DPN non deformed feet	Median 64 (44-78)	unknown	11 varying insoles	n/a	

Table 2.1 (continued) Characteristics of included studies

(Hastings *et al.*, 2007)[37]	US	Cohort study	n=20 DPN	57.3 (9.3)	12:8	3 insole conditions	n/a	At 2nd MTPJ: PPP↓ (32%) when pad placed between 6.1 & 10.6mm proximally; PPP ↓(16%) when pad located 1.8mm distal to 6.1mm proximally; PPP↓ (57%) when distal part of met pad was 10.6mm proximal to met head; PPP↑ when pad was further than 1.8mm distally or >16.8mm proximally.
(Hsi, Chai & Lai, 2002)[39]	Taiwan	Cohort study	n=14 DPN	61.4 (8.3)	6:8	Patients' own shoes	n/a	Diabetic footwear: Pressure time integral (↓heel), (↓anterior to MTPJ), (↓at toe regions) (↑at the midfoot & posterior to MTPJ) PPP: (↓heel), (↓anterior to MTPJ), (↓at toe regions), (↑midfoot & posterior to MTPJ).
(Hsi, Chai & Lai, 2004)[40]	Taiwan	Cohort study	n=10 DPN	63(9)	3:7	Patients' own shoes		Rocker sole ↓PPP & pressure time integrall in anterior lateral, central lateral & central medial forefoot & prolonged time to PPP in posterior forefoot but not anterior forefoot.

Table 2.1 (continued) Characteristics of included studies

(Kastenbauer *et al.*, 1998)[41]	Austria	Cohort study	n=13 DM	56(8)	5:8	Leather styled Oxford shoe	n/a	At great toe PPP ↓ with: cork insole & in-depth shoe (16%), Adidas shoe(32%); CMI & in-depth shoe (33%); At 1st MTPJ PPP ↓ with: cork insole & in-depth shoe (27%), Adidas shoe(29%); CMI & in-depth shoe (50%); At 2/3rd MTPJ PPP ↓ with: cork insole & in-depth shoe (19%), Adidas shoe(47%); CMI & in-depth shoe (48%); At heel PPP ↓ with: cork insole & in-depth shoe (34%), Adidas shoe(34%); CMI & in-depth shoe (39%).
(Lavery *et al.*, 2012)[42]	US	Single physician blinded RCT	n=299 DPN previous ulceration or neuropathy & foot deformity	Shear group 69.4(10.0); Standard group71.5 (7.9)	202:97	Insoles for standard treatment	18 months	3.5 times odds of developing an ulcer; 3 ulcers developed in shear resistant insole group, 10 ulcers developed in standard insole group

Table 2.1 (continued) Characteristics of included studies

(Lin *et al.*, 2013)[43]	Taiwan	Cohort study	n=26 DPN	68 (9)	10:16	Standard shoe with insole	n/a	For regions of interest: 15.7% ↓Mean PPP (pre-plug removal); 32.3% ↓Mean PPP (post vs post plug removal); 14.3% ↓Mean PPP (arch addition to pre plug removal vs post plug removal). For Non-regions of interest 8.7% ↓Mean PPP (pre-plug removal vs barefoot); 2.2% ↑Mean PPP with pre vs post plug removal); 2.5% ↓Mean PPP (arch addition to pre plug removal vs post plug removal).
(Lobmann *et al.*, 2001)[44]	Germany	Case control	n=81 type 2 DM (n=18 DPN & high forefoot pressures vs n= 63 (control)	Intervention group 63(9); control group 66 (10)	Unknown	Neutral shoes	8 weeks & 6 & 12 months	32.6% ↓Maximum PPP at issue 28% ↓ Maximum PPP at 6 months; 13% ↓ Maximum PPP at 12 months.
(Lopez-Moral *et al.*, 2019)[70]	Spain	RCT	N=51DPN and previous foot ulceration	Intervention group 61 (8.1); control group 60 (8.6)	Intervention group 24:2; Control group 23:2	Semi-rigid rocker	6 months	Rigid rocker sole ↓ re-ulceration risk by 64%

Table 2.1 (continued) Characteristics of included studies

(Lott *et al.*, 2007)[45]	US	Cohort study	n=20 DPN & history of ulceration	57.3 (9.3)	12:8	Barefoot	n/a	Mean applied pressure: barefoot (272 kPa); shoe (173 kPa), shoe & CMI (140 kPa); CMI & metatarsal pad, (98 kPa). Soft Tissue Strain at 2nd MTPJ: barefoot (38.2%), shoe (31.6%); shoe & CMI (28.9%); shoe, CMI & Metatarsal Pad (24.1%).
(Martinez-Santos, Preece & Nester, 2019)[71]	UK	Cohort study	n=60 DPN	67(13)	40:20	Flat insole	n/a	PPP ↓ of 29KPa with metatarsal bar and EVA/poron materials
(Mohamed *et al.*, 2004)[46]	US	Case series comparison	n=16 DPN Type 2 (n=8 Plastazote vs n=8 Plastazote/Aliplast)	Plastazote group 68.4 (5.5); Plastazote /Aliplast group 68.9(5.5)	8:8	No insole	1 month & 3 months	With CMI at baseline: decrease in PPP (12.0 N/cm²); Max Mean Pressure (4.9 N/cm²); Pressure Time Integral (5.6 N/cm²/s) & ↑Total Contact Area (21.2cm²). At follow up: decrease in PPP (10.5 N/cm²); Maximum mean pressure (5.2 N/cm²) & Pressure Time Integral (5.9 N/cm²/s) & ↑ Total Contact Area (20.2cm²).

Table 2.1 (continued) Characteristics of included studies

(Mueller *et al.*, 2006)[47]	US	Cohort study	n=20 DPN & history of forefoot ulcer	57(9)	12:8	Shoes with standard insoles	n/a	19-24% PPP↓ (CMI), 15-20% PPP↓ (CMI +metatarsal pad); 16-23% Pressure Time Integral ↓ (with CMI), 22-32% Pressure Time Integral↓ (CMI +metatarsal pad & shoe).
(Nouman, Leelasamran & Chatpun, 2017)[66]	Thailand	Cohort study	n=16 DPN	58(9)	9:7	Without CMI	n/a	PPP↓26% at forefoot and 24% at toes with CMI
(Nouman *et al.*, 2019)[72]	Thailand	Cohort Study	N=16 DPN	unknown	9:7	Addition of multifoam top cover	n/a	forefoot maximum PPP 248.2kPa (61.92) with CMI; 211.6k Pa (47.01) with CMI and multifoam
(Owings *et al.*, 2008)[48]	US	Cohort study	n=22 DPN & high pressures (>750kPa) in MTPJ region	63.7(10.7)	11:11	Polypropylene shell with Korex sponge or plastazote cover; EVA shore 45 with procell or plastazote cover.	n/a	168kPa PPP at regions ff interest (shape based & pressure informed CMI); 211kPa PP (CMI shape based & 45 Shore EVA base with Procell or Plastazote top cover); 246kPa PPP (CMI polypropylene shell with Korex, sponge or plastazote top cover); In rocker shoes: 127 kPa PPP at regions of interest (shape based & pressure informed CMI) Plastazoze.

Table 2.1 (continued) Characteristics of included studies

(Parker *et al.*, 2019)[73]	UK	RCT	n=57DPN	Traditional group 61.4 (10), digital group 66.3 (10.5)	45:7	Control insole 3mm poron	6 months	Compared with control insole PPP ↓14.91% with traditional insole and ↓24.43% with digital insole at baseline
(Paton *et al.*, 2012)[50]	UK	RCT	n=119 DPN	custom group 71(10) prefab group 70(10)	90:29	Pre-fabricated contoured shell	6 months	With CMI (37% ↓PPP at baseline & 6 months); (27% ↓Pressure Time Integral at baseline & 30% at 6 months); (32% ↑Total Contact Area baseline & 15% at 6 months). With Prefabricated insole: (35% ↓PPP at baseline & 31% at 6 months); (22% ↓Pressure Time Integral & 24% at 6 months); (29% ↑Total Contact Area at baseline & 15% at 6 months); No difference between CMI & prefabricated insole in PPP & Total Contact Area
(Paton *et al.*, 2014b)[49]	UK	Observational cohort study	n=60 DPN	69	47:22	Pre-fabricated contoured shell	3, 6,12 months	↓PPP with CMI of 39% (0 months), 35% (6 months) & 36% (12 months)

Table 2.1 (continued) Characteristics of included studies

(Perry *et al.*, 1995)[51]	US	Cohort study	n=39 total: 13 DM, 13 DPN, 13 non diabetic	DM group 53.6(9.4); DPN group 52.8(7.3); Non diabetic group 54.2(9.7)	33:6	Sock only	n/a	Oxford shoes vs socks: 18% ↓Mean PPP (2nd MTPJ), 2.3% ↓Mean PPP (MTPJ's & heel); Running shoe vs socks 31% ↓Mean PPP (forefoot & heel)
(Praet & Louwerens, 2003)[52]	Netherlands	Cohort study	n=10 DPN	63 (44-78)	0:10	Oxford shoe without insole	n/a	3 Oxford type shoes show no significant ↓ in pressure vs baseline; rocker bottom shoes showed ~50% ↓PPP in central forefoot vs no rocker; mean ↑Total Contact Insole with insole (3.4-7.3 cm²)
(Preece *et al.*, 2017)[67]	UK	Cohort study	n=102 DM at low risk and n=66 healthy control	57(9)	52:50	8 shoe conditions	n/a	Optimum location of 52% apex, 20˚angle and apex 95˚

Table 2.1 (continued) Characteristics of included studies

(Raspovic *et al.*, 2000)[53]	Australia	Cohort study	n=8 DPN with past ulceration	61(48-68)	8:0	No insole	n/a	↓PPP, Pressure Time Integrals & ↑Total Contact Area
(Reiber *et al.*, 1997)[54]	US	Cohort study	n=24 DPN no history of ulceration	66(9.3)	unknown	Preformed insole	Up to 6 months	0 breaks in skin at 6 months
(Reiber *et al.*, 2002)[55]	US	RCT	n=400 DM with history of foot ulceration	62	309:91	Usual footwear	2 years	Number of feet ulcerated 15% (shoes & cork insoles), 14% (shoes & prefabs), 17% (control group)
(Rizzo *et al.*, 2012)[56]	Italy	RCT	n=298 DM at high risk	Standard group 66.2 (9.4) intervention group 68.1(14.1)	unknown	Standard care	12 months, 3 & 5 years	Foot ulceration development: At 12 months 13% (intervention) vs 38.6% (standard care). At year 3, 18% (intervention) vs 61% (standard care); At year 5, 24% (intervention) vs 72% (standard care)
(Sacco, Akashi & Hennig, 2010)[57]	Germany	Cohort study	n=45 participants (21 control, 24 DPN)	DPN 55.2(7.9) Control group 50.9 (7.3)	unknown	barefoot	n/a	1st Ground Reaction Force peak > during shod conditions & > propulsion force in diabetic group but 2nd Ground Reaction Force peak < in shod diabetic vs control group

Table 2.1 (continued) Characteristics of included studies

(Scherer, 1975)[58]	US	Cohort study	n=7 insulin taking DM patients	38(28-59)	3:4	n/a	10 weeks	6 patients discontinued use of footwear (5 plantar irritation of heel & 1 hypertrophic lesions under 4/5th MTPJ's)
(Soulier, 1986)[59]	US	Cohort study	n=108 DM Caucasian non-smokers	55(19-55)	33:45	Own shoes	monthly	Significant change in callus size with running shoes
(Hellstrand Tang *et al.*, 2014)[38]	Sweden	RCT	n=114 DPN & previous ulceration	58 (15)	62:52	Prefabricated insole	2 years	PPP= 180kPa (35 EVA insole); 189kPa (55 EVA insole); 211kPa (prefab)
(Telfer *et al.*, 2017)[68]	UK	Cohort study	n=20 DPN	64.4(9.2)	15:5	Barefoot	n/a	Optimised milled lowered PP by 41.3Kpa compared to CMI and optimised printed lowered PPP by 40.5kPa compared to CMI.
(Tsung *et al.*, 2004)[60]	Hong Kong	Cohort study	n=6 DPN vs n= 8 control	DPN group 56.2(6.2); control group 46.5(11.7)	unknown	Shoe-only	n/a	Mean PPP↓ 13.4% (Non Weight Bearing insole), 13.8 % (Semi Weight Bearing insole), 8.1% (Fully Weight Bearing insole), 2.4% (flat insole)

Table 2.1 (continued) Characteristics of included studies

(Uccioli *et al.*, 1995)[61]	Italy	RCT	n=69 high risk/past ulcer	Pod group 59.6(11); Control 60.2(8.2)	43:26	Non-therapeutic shoes	12 months	Ulcer relapse 58.3% (control) vs 27.7% (intervention)
(Ulbrecht *et al.*, 2014)[62]	US	RCT	n=150 DPN recently healed ulcer	Experiment group 60.5(10.1); Control group 58.5(10.7)	104:46	Standard insoles	15 months	Ulcer occurrence control> insole; no difference in non-ulcerated lesion.
(Viswanathan *et al.*, 2004)[63]	India	Case control	n=241 DM previous foot ulceration	Gr1=59.1 (8.2);Gr2-54.5(9.1); Gr3=53.9(9.3);Gr4= 59.1(11.7)	156:85	Usual footwear	9 months	PPP↓ 57% (MCR insole); 61% (Polyurethane); 58% (moulded footwear) 39% (own shoe)

Table 2.1 (continued) Characteristics of included studies

(Waaijman *et al.*, 2012)[64]	Netherlands	Cohort study	n=117 DPN (85 experimental vs 32 control)	63.3(10.1)	unknown	Pre & post modification	3 monthly until 1 year	PPP↓ 23% (ulcer site) & 21% (highest PPP site)
(Wrobel *et al.*, 2014)[65]	US	Cross-sectional analysis	n=27 DPN pre-ulcer callus/past ulceration	65.1	14:13	Standard control insoles	n/a	↓Temperature of 64.1% (forefoot) & 48% (midfoot) with DFO

US-United States, UK –United Kingdom, DPN – diabetic peripheral neuropathy, DM – diabetes Mellitus, ↓-decrease, ↑increase, n/a – not applicable, CMI- Custom made insole, PPP-peak plantar pressure, MTPJ – metatarsal phalangeal joints, direction of change refers to the intervention group

2.4.5 Description of outcome measures

Twenty percent (n=11) of studies [29,34,42,54-56,58,61,62,70,77] reported foot lesions and ulceration as the primary outcome measure. Measurement of this outcome varied across all of the studies, with only one study 54 using a validated wound classification system; six studies [34,42,55,62,70,77] used a broad definition of 'lack of skin integrity through loss of the epidermis and dermis' and the remaining studies had no definition of an ulcer or lesion [29,56,58,61]. All of these studies used professional judgement to assess for the presence of ulceration, although two of the studies [55,62] used photographs as a means of blinded assessment. Four percent (n=2) studies [31,59] used the presence of callus as the primary outcome measure, one study [31] applied a non-validated grading system to assess callus condition, whilst the other [59] measured diameter and thickness of callus lesion. One study [57] reported ground reaction force (GRF) and electromyographic (EMG) activity of three muscles as outcome measures. One study [65] used temperature (°C) as an outcome measure, inferring a rise in temperature with increased risk status when testing the shear reduction device. Seventy two percent (n=39) of studies [20-27,30,32,33,35-41,43-53,57,60,63,64,66-68,71-73] used kinetic outcomes to evaluate the effectiveness of the footwear and insole intervention provided. However, there was considerable inconsistency in the measures amongst these studies, with mean peak pressure, maximum pressure, maximum mean pressure, mean total pressure, pressure time integral and force time integral all used.

2.4.6 Profile/shape of the insole, shoe upper and shoe outsole

Two features of insole profile were described in the majority of studies; arch profile and rocker profile. In total, 69% (n=37) of studies [20-29,34,36-38,41,43-46,48-51,53-56,58-64,66,68,73] reported using an arch profile as a feature of an insole (electronic supplementary material 3) and 37% (n=20) of studies [26,28-30,34,35,38,40,48-50,52,54-56,61,64,65,67,70] reported rockers as an added feature of the shoe outsole (electronic supplementary material 4). One study [39] lacked enough clarity in the description of the intervention to determine if a rocker feature was used in the diabetic footwear.

Only ten percent (n=5) repeated measure studies [21,24,36,43,60] measured the direct effect of an arch profile on mean peak pressure. According to the heterogeneity test, high heterogeneity existed (I^2=81%, χ^2 =13.6, τ^2 = 1160, p=0.009). Therefore, random effects modelling was applied to consolidate the effect value. Figure 2.2 shows that that out of 119 participants, the addition of an arch profile reduced peak pressure by a mean of 37 kPa (MD, -37.5; 95% CI, -72.29 to -3.61; $p < 0.03$) when compared to a flat insole. For the remaining 31 studies [20,22,23,25-29,34,37,38,41,44-46,48-51,53-56,58,59,61-64,66,68] who reported using the arch profile as a feature of the insole, meta-analysis was not conducted due to an inability to isolate the effect of this feature from other features of the insole.

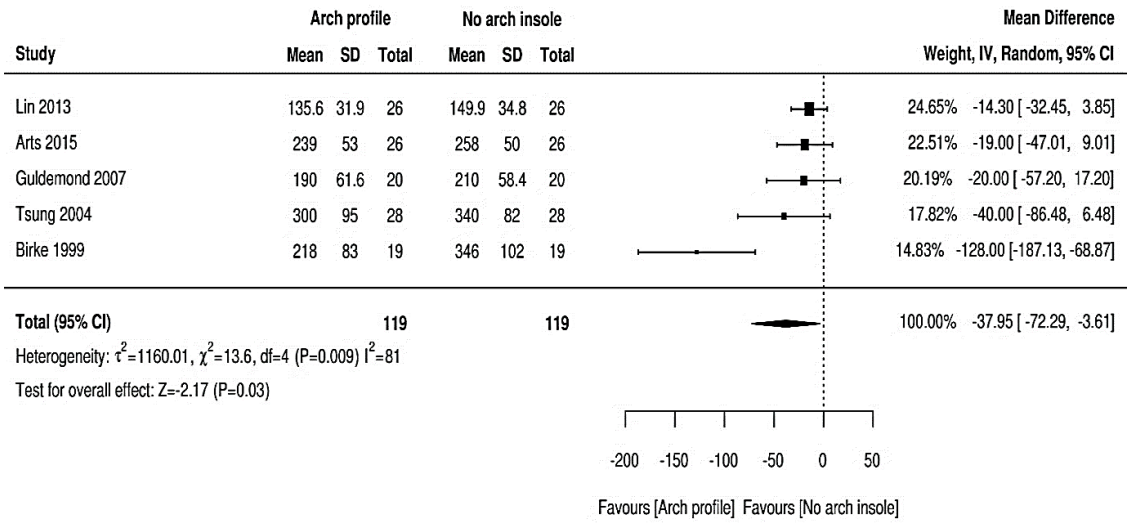


Figure 2.2 Meta-analysis of arch profile

Four studies reported the effect of a rocker profile. One study reported that in 71-81% of participants tested an optimum peak pressure target value of under 200kPa could be achieved with a combination of apex position at 52% of shoe length and rocker angle of 20° [67]. Another study reported no interaction effect when altering apex angle, apex position and rocker angle compared to the control shoe [30]. A third study reported decreases in peak pressures and pressure time integrals in the posterior and anterior, central lateral and central medial forefoot with a standardised rocker shoe with apex position (83mm on medial and 87mm on lateral from front of shoe), angle thickness (24mm maximum thickness at rocker with 11mm rocker height at front end) compared to shoe without rocker [40]. A fourth study reported ulcer re-occurrence to be 64% with a semi-rigid rocker sole compared to 23% with a rigid rocker sole [70]. There was an inability to distinguish the effect of the rocker profile feature from other features of the footwear and insole for those remaining studies [26,28,29,34,35,38,48-50,52,54-56,61,64,65].

2.4.7 Modifications made to the insole and shoe outsole

Sixty-five percent (n=35) of studies [20-22,24,26,31,33,34,37,39,41,43,44,49,50,52-56,58,60-62,65,70] reported modification of footwear, although no separation of this feature from others would allow a pooled effect analysis to occur (electronic supplementary material 5). Fourteen studies [20-22,24,26,34,37,41,43,52,56,60-62] reported using extra-depth shoes as a modification, five studies used diabetic footwear [31,39,43,49,50] and one study [60] reported patient specific footwear, customised to the individual, but did not report the effect this had on any outcome measure.

Thirty-three percent (n=18) of studies [21-23,26,27,36-38,45-48,56,62,64,68,71,73] reported the use of metatarsal addition to the insole (supplementary material 6). Only three repeated measure studies [21,36,45] could distinguish the effect of a metatarsal addition independently from other insole and footwear features and were used for the meta-analysis. According to the heterogeneity test, high heterogeneity existed (I^2=0%, χ^2 =0.34, τ^2 = 0, p=0.844). Therefore, random effects modelling was applied to consolidate the effect value. Figure 2.3 shows that out of 70 participants, the use of a metatarsal addition in an insole reduced mean peak pressure by a further 35.96 kPa (MD, -35.96; 95% CI, -57.33 to -14.60; p < 0.001) when compared to an insole without metatarsal addition. There was a lack of description of the metatarsal addition and no clear indication of how or when to utilise it as a modification.

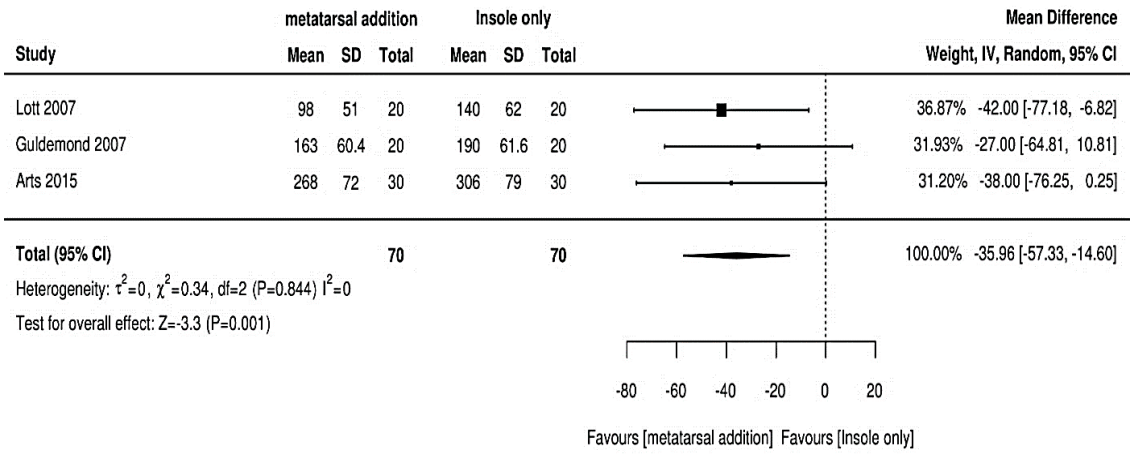


Figure 2.3 Meta-analysis of metatarsal addition

Twenty-two percent (n=12) of studies [21,22,26,27,34,43,48,53,64,68,70,73] modified insoles with the use of a cut out or aperture to target the site or lesion under the foot of clinical interest (electronic supplementary material 7). However, only two studies [21,43] reported the direct effect of this feature. Arts (2015) reported the reduction of in-shoe peak pressure of 21kPa from 253(48) kPa to 232(54) kPa with the removal of material in the insole for a variety of target locations [21]; and Lin reported reductions of MPP at regions of interest (ROI) located in the forefoot by 72kPa from 221.4(50.3) kPa to 149.9(34.8) kPa with the removal of 1cmx1cm² plugs from underneath ROI [43].

Thirteen per cent (n=7) of studies [27,31,33,36,42,73,77] used 'other' modifications. One study reported a 71% reduction on ulcer incidence when using 'intelligent' insoles with pressure detecting sensors compared to the control group [77]. One study reported a 9kPa reduction in mean peak pressure when adding a custom made five degree full length varus and valgus cork posts to the base of the insole for 20 participants with diabetic peripheral neuropathy and non-deformed

feet [36]. The remaining studies did not report the effect of these modifications. One study reported balancing the ¾ length orthotic with the use of dental acrylic posts at the rearfoot [31] and another study used extra-density padding at the heel, forefoot and covering the toes as a modification [33]. Another study reported the use of wedge or medial skive on two occasions, prescribed at the discretion of an orthotist, but no rationale for use provided [73]. One study reported including elastic binders and two non-stick sheets placed between the upper and lower pad of the insole as part of their shear resistant insole [42] and one study used substantial heel cups in the design of their insole, although no specification was disclosed [27].

2.4.8 Fabrication techniques used for the insole and shoe

Forty-three per cent (n=23) of studies [20-22,25-27,31,37,38,45,48-50,54-56,60,61,63,65,66,68,72,73] used casting techniques to fabricate the insole and shoe (electronic supplementary material 8) and 20% (n=11) of studies [21,26,27,34,36,43,48,54,56,64,73] used kinetic information to inform the fabrication of the insole or shoe (electronic supplementary material 9). One study used both a 'traditional' foam box casting technique and a weight bearing foot scan technique [73]. Another study [44] used a pedorthist to prepare the insoles individually, although no further information was reported and one study [29] reported the manufacture of the shoe by a local shoemaker according to an algorithm, but did not disclose the technique of the insole fabrication. Three studies [23,49,50] used preformed insoles.

Only one repeated measures study [60] reported effects of casting techniques to manufacture insoles under different loading conditions. Therefore, pooled analysis was not possible due to the diversity of techniques and lack of reported

outcomes. Tsung et al [60] reported decreases in MPP compared to shoe only condition of 13.4% when casted non-weight bearing, 13.8 % when casted with a semi-weight bearing insole, 8.1% when casted with a full weight bearing insole, and 2.4% with a flat insole.

Twenty per cent (n=11) of studies [21,26,27,34,36,43,48,54,56,64,71] used kinetic analysis to inform the design and modification of the insole (electronic supplementary material 9). Only one study [56] used ulceration as an outcome measure, the remainder using kinetic measures. Four repeated measure studies [26,43,48,64] reported the direct effect of using plantar based pressure analysis as a fabrication technique to inform the design and modification of the insole and shoe in reducing mean peak pressure. According to the heterogeneity test, high heterogeneity existed (I^2=93%, χ^2 =63.98, τ^2 = 2565.09, p=0). Therefore, random effects modelling was applied to consolidate the effect value. Figure 2.4 shows that in 189 participants, MPP in insoles fabricated with the use of an in-shoe system was reduced by 75.4kPa (MD, -75.4kPa; 95% CI, -127.4kPa to -23.44 kPa; $p < 0.004$) compared to those insoles fabricated using traditional techniques not involving pressure measurement systems.

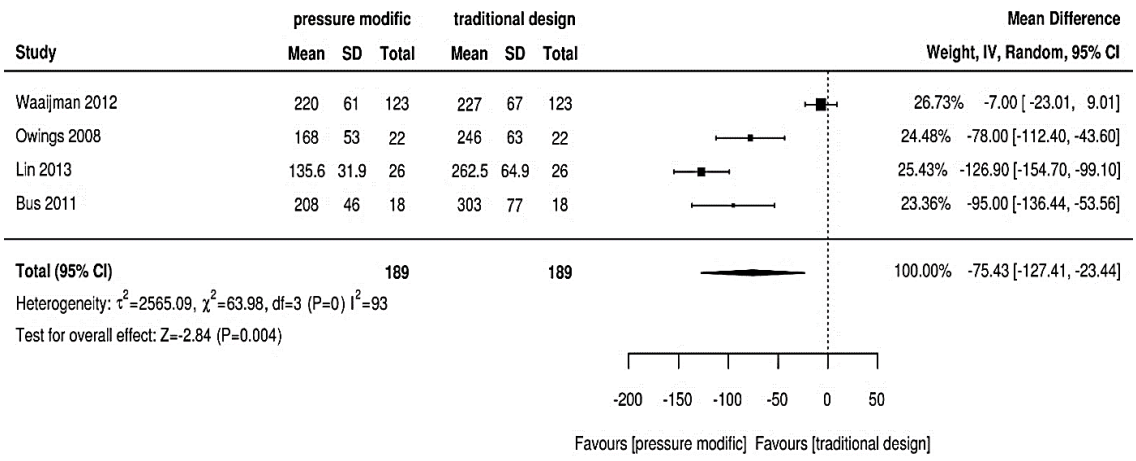


Figure 2.4 Meta-analysis of pressure modified insoles

2.4.9 Material type and properties of the insole and shoe outsole

Sixty-nine percent (n=37) of studies [21-23,25-30,34,36,41-44,46,48-50,52-56,58,60-66,68,70-73] used a combination of materials with diverse properties to manufacture the insoles or shoe outsole (electronic material supplementary 10). Thirty per cent (n=16) of studies [20,23,27,29,34,35,46,48-50,52,54,55,58,60-62,68] used dual density constructs, thirty-nine percent (n=21) of studies [21,22,25,26,28,30,36,41-44,52,53,56,63-66,70,72,73] used tri or multi-density/layers. Five studies examined the influence of material on reducing MPP. One RCT [38] of 114 DPN participants directly examined the effectiveness of CMI's constructed of different materials. Comparisons of kinetic variables for a 35 shore Ethyl-Vinyl Acetate (EVA) CMI with a 55 shore hardness EVA CMI and a prefabricated insole (GloboTec, Comfort 312750501400) all within a standardised walking shoe were reported. The main pressure reduction between the CMI and the prefabricated insoles was achieved at the heel and in the overall peak pressure of 180kPa with the extra soft durometer 35 shore hardness EVA insoles as opposed to 189kPa for

the soft 55 shore hardness EVA insole. The second study reported no statistical differences in reducing plantar pressures when comparing orthoses constructed of a single density material, Plastazote (Zotefoams Inc., Walton, KY) with a dual density material, Plastazote and Alliplast (Voltek, Brennia, VA) [46]. The third repeated measures study reported a significant difference in MPP between different densities of poron in walking conditions ($p<0.0001$) [24] although another study found no difference between Poron 96 and Poron 4000 in reducing peak pressure [32]. A fifth study reported the reduction of maximum peak pressure at the forefoot with the addition of a multifoam top cover onto the dual density custom made insole of plastazote and microcellular rubber [72].

2.5 Discussion

The aim of this review was to identify the best footwear and insoles design feature for offloading the plantar surface of the foot to prevent foot ulceration in people with diabetes. More specifically, the objectives were to identify the key design features of footwear and insoles with regard to profile and shape, material type and properties, modifications and fabrication techniques.

Heterogeneity was found amongst the profile, modifications, material and fabrication techniques used in insoles and footwear design. Footwear and insoles can be viewed as multifaceted interventions where several features are frequently incorporated into the design. The studies highlighted the lack of a systematic approach to combining these features which makes it difficult to distinguish the effectiveness of individual features in offloading plantar foot pressures.

Within the review, we revealed variations in outcome measures, study design and quality. Six different outcome measures were used amongst the studies which makes meaningful comparison difficult. Identification of specific design features of footwear and insoles related to the primary outcome measure of foot ulceration was not possible. This was because all of the studies using foot ulceration as the outcome measure employed a combination of footwear and insole design features. The follow up time-points at which outcomes were measured varied considerably across studies. The methodological quality of the studies was generally poor. Only four studies [21,38,50,73] reported adherence to the insoles and footwear with one study excluding participants from analysis where there was a lack of substantial wear [73]. The inclusion criteria contained participants with diabetes who were at different stages of disease progression, further adding to the difficulty in making meaningful comparisons between studies. Some studies included people with no sensory neuropathy; some studies included those with sensory neuropathy and no previous foot ulceration and some studies included participants with sensory neuropathy and previous foot ulceration. Foot complication severity has been shown to be associated with increased plantar foot pressures [10]. However, this did not appear to influence the footwear or insole feature used.

2.5.1 Profile/shape of the insole, shoe upper and shoe outsole

Two types of profile features were described in this review; an arch and a rocker. The use of an arch profile replicating the contour of the plantar surface of the foot has traditionally been the ‘gold-standard’ for insole design for reducing pressure in the diabetic neuropathic foot [78]. This review found that

98% of studies reported using an arch profile as part of the insole configuration, although inconsistency exists in the reporting of the specifications. Our meta-analysis provides evidence that an arch profile when added to an insole can enhance the offloading effect by a further 37kPa when compared to an insole without an arch profile. It is postulated that by increasing contact with the plantar surface of the foot, thereby allowing an increased distribution of force over a greater area of the foot, plantar foot pressure will be reduced [79]. Our review demonstrated that seven studies incorporating an insole with an arch profile reported that an increase in surface contact area values correlates with reduced forefoot pressures [20,23,46,49,50,53,60]. However, Paton et al. reported that the increase in total contact area observed at issue, reduced by 50% after six months of insole wear, whilst pressure reduction remained constant [49,50]. The authors suggest that this could be attributed to the dynamic nature of gait and associated pressure reduction may be associated with changes in foot function, such as the prevention of foot pronation [80,81].

Nineteen studies modified the rocker profile of the shoe as a method of reducing peak pressure. The rigid sole added to the bottom of the shoe is designed to limit the movement at foot joints, particularly extension of the metatarsophalangeal joints at the propulsive phase of gait. This prevents movement of tissue across the plantar aspect of the foot and alters the forefoot loading pattern, specifically reducing pressure under the metatarsal heads by 30% to 50% [82,83]. Our review demonstrates the multiplicity of design variables in terms of rocker angle, placement, height and material. Preece et al., suggested an optimum design of a rocker, but reported further adjustments of rocker angle and position reduced pressure on the forefoot across the participants [67].

Chapman et al [30] reported high inter-subject variability for apex position in reducing pressure under the 1st MTPJ and hallux regions with no clear optimal position. Some consistency was achieved with reducing pressure under the 2nd to 4th MTPJ with an apex position of 50-60% of shoe length. The use of a rocker profile could be beneficial in reducing peak pressure under the diabetic neuropathic foot. However, the effectiveness of this feature may correlate with an individualised approach in the design of the rocker angle, placement, height and material, although no such design algorithm has yet been established.

2.5.2 Modifications

The purpose of modifications is to further adapt the footwear and insole by additional features. Three key modifications of insole and footwear design features were identified from this review; extra-depth footwear, metatarsal additions and sinks or apertures. However, the inability to distinguish the effect of individual modifications from other insole and design features for the majority of studies creates uncertainty on the effectiveness of their usage. Additionally, the assortment of each modification with variations in design, materials, placement and fabrication made direct comparison extremely difficult. Despite this heterogeneity meta-analyses verified the positive effect of metatarsal pad, cut-outs or apertures in reducing forefoot plantar pressures. However, the effectiveness in reducing plantar pressure varies considerably with placement of the modification. For example, Hastings et al., established a pattern of increases or decreases in MPP according to placement of the metatarsal pad proximal or distal to the metatarsal, although only an effect on the 2nd metatarsal head was observed [37]. A data driven approach using real time

plantar pressure feedback, as utilised by 10 studies [21,26,27,34,36,43,48,54,56,64] intimates that the effectiveness of some modifications could be enhanced by more accurate siting using appropriate technology, such as real time pressure analysis.

2.5.3 Fabrication techniques used for the insole and shoe

Two different fabrication techniques for insoles and footwear were identified in this review; casting, and kinetic informed. Casting is traditionally used to capture the geometric shape of the patient's' foot to 'customise' the insole. Only one study examined the role of three types of casting technique in reducing peak pressure [60]. The authors reported an insole formed from a semi-weight bearing foot shape offered the greatest peak pressure reduction compared to full weight bearing and non-weight bearing foot shapes, but was not statistically significant. The remaining studies using a casting approach were not able to report any difference in reducing pressure using this fabrication method. This method of fabrication is believed to create an arch profile, which has been demonstrated as altering pressures in the plantar foot as reported by four studies [21,24,36,60]. However, one author, Paton et al., 2011, demonstrated no difference in reducing MPP and PTI when using a prefabricated insole compared to a customised insole [50]. Therefore, potentially all insoles with an arch profile, regardless of the casting technique employed, are effective in reducing plantar pressure in people with diabetes. This view complements another finding of this review that suggests an arch profile may optimise the effect of insoles for diabetic feet.

Ten studies [21,26,27,34,36,43,48,54,56,64] reported the effect of using in-shoe pressure measurement analysis to guide the fabrication of the footwear and insole. The use of a data driven approach for insole and footwear design has been heralded as authenticating plantar foot pressure reduction on an individual basis. Identification of the vulnerable plantar areas with pressure mapping, guides the design and alteration of appropriate personalized footwear and insoles in terms of materials, geometry and modifications. In addition, it provides a quantitative assessment of clinical outcome such that clinicians can be certain of achieving the desired treatment objective. Our meta-analysis supports this proposition although variations in methodology with this technique requires a more consistent approach to limit the inconsistency across clinical areas. Only one study [54] used pressure data to inform the design of the insoles; the remainder used the kinetic data to inform the modification of the insoles by iteratively testing and retesting until optimisation was reached. A lack of standardisation existed across all of the studies for temporal-spatial measurements and gait parameters contributing to the analysis. The use of different pressure analysis systems with dissimilar technical specifications and resolution provides additional inconsistency. Furthermore, it should be acknowledged that foot plantar pressure values are only considered a surrogate measure of foot ulceration risk, and that no threshold for foot ulceration has yet been established [84].

2.5.4 Material type and properties of the insole and shoe outsole

Material choice is an important feature of any insole or footwear design. The material used, dependent on its mechanical and physical properties, will

influence the insole or footwear's ability to redistribute or dampen forces effectively. This review found no consistency with individual materials used or thickness in the construction of footwear or insole. Only one study directly assessed the effect of material hardness in reducing peak plantar pressures [38]. Sixty-seven per cent of remaining studies used either dual or multi-density material constructions of footwear and insoles. Closed cell foam materials were most frequently sited at the interface between foot and insole and footwear as a top cover; denser materials constituted the base of the insole, EVA appearing the most popular material of choice for the base. A less popular material type was thermoplastics, potentially because these materials were traditionally used for functional devices aimed toward changing gait function and not reducing pressure. Combining materials of different properties is suggested as incorporating the desired properties from each material to best serve reduction in foot ulceration risk [85-87]. However, the literature does not provide a sufficiently robust evidence base to inform the selection approach regarding material combination or thickness for the best offloading. Therefore, selection of materials is often influenced by the availability of materials locally and anecdotal evidence, rather than patient specific characteristics and effectiveness of offloading.

2.6 Limitations

The primary limitation of this review is the heterogeneity of study design and outcome measures of the studies included. Large variations in the description of footwear and insoles and uncertainty in the reliability and validity of the assessment and intervention methods exists. The diversity of features used

limits the generalizability of the results, resulting in variation in the number of studies and participants included within the meta-analyses. This review was further limited by the inclusion of only English language studies, not including trial databases in the search database and exclusion of participants with charcot and foot amputation.

2.7 Recommendations

A consensus is required regarding how to report and measure the effectiveness of individual insole and footwear features in offloading the DPN foot. A core set of outcome measures and standardized time points would facilitate pooling of results in meta-analyses to enable more accurate conclusions to be drawn. Standardization of inclusion criteria is further required to ensure all participants enrolled in offloading trials of DPN have DPN. This would also include participants with charcot and foot ulceration. Improved consistency in the reporting of methodology, in line with the Consolidated Standards of Reporting Trials guidelines and International working group on the diabetic foot, is also recommended [84].

2.8 Conclusion

This systematic review highlights the difficulty in differentiating insole and footwear features in offloading the neuropathic diabetic foot. The amalgamation of features in insole and footwear designs makes consolidation of the body of knowledge difficult for understanding which feature to use at which time point. However, on the basis of this review we conclude that metatarsal additions, apertures and arch profiles are effective in reducing plantar pressure in this population, and therefore should be incorporated as footwear and insole

features. Different casting techniques and materials also appear effective in reducing pressures, but we are unable to recommend any particular technique or type because of insufficient evidence. The use of pressure analysis to enhance the effectiveness of the design of footwear and insoles, particularly through modification, is recommended, specifically in patients with diabetes and peripheral neuropathy.

2.9 Conflicts of interest

Richard Collings is funded by a National Institute for Health Research (NIHR) Clinical Doctoral Fellowship for this research project. This publication presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

2.10 Acknowledgements

I am grateful for the assistance of the University of Plymouth librarians for their assistance with the search strategy.

2.11 Ethics approval

This review manuscript summarizes and informs of already published studies and thus does not require ethical approval.

2.12 Data availability statement

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

2.13 References

1. Schaper NC, Van Netten JJ, Apelqvist J, Lipsky BA, Bakker K. Prevention and management of foot problems in diabetes: A Summary Guidance for Daily Practice 2015, based on the IWGDF guidance documents. Diabetes Res Clin Pract. 2017;124:84-92.

2. Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. The New England journal of medicine. 2017;376(24):2367-2375.

3. Driver VR, Fabbi M, Lavery LA, Gibbons G. The costs of diabetic foot: the economic case for the limb salvage team. J Vasc Surg. 2010;52(3 Suppl):17s-22s.

4. Kerr M, Barron E, Chadwick P, et al. The cost of diabetic foot ulcers and amputations to the National Health Service in England. Diabetic Medicine. 2019.

5. Paisey RB, Abbott A, Paisey CF, Walker D. Diabetic foot ulcer incidence and survival with improved diabetic foot services: an 18-year study. Diabetic medicine : a journal of the British Diabetic Association. 2019.

6. Pound N, Chipchase S, Treece K, Game F, Jeffcoate W. Ulcer-free survival following management of foot ulcers in diabetes. Diabetic medicine : a journal of the British Diabetic Association. 2005;22(10):1306-1309.

7. Bus SA, Waaijman R, Arts M, et al. Effect of custom-made footwear on foot ulcer recurrence in diabetes: a multicenter randomized controlled trial. Diabetes care. 2013;36(12):4109-4116.

8. Bus SA, van Netten JJ. A shift in priority in diabetic foot care and research: 75% of foot ulcers are preventable. Diabetes Metab Res Rev. 2016;32 Suppl 1:195-200.

9. Waaijman R, de Haart M, Arts ML, et al. Risk factors for plantar foot ulcer recurrence in neuropathic diabetic patients. Diabetes care. 2014;37(6):1697-1705.

10. Fernando ME, Crowther RG, Pappas E, et al. Plantar pressure in diabetic peripheral neuropathy patients with active foot ulceration, previous ulceration and no history of ulceration: a meta-analysis of observational studies. PloS one. 2014;9(6):e99050.

11. Fernando ME, Crowther RG, Lazzarini PA, et al. Plantar pressures are higher in cases with diabetic foot ulcers compared to controls despite a longer stance phase duration. BMC Endocr Disord. 2016;16(1):51.

12. Fernando ME, Crowther RG, Lazzarini PA, et al. Plantar pressures are elevated in people with longstanding diabetes-related foot ulcers during follow-up. PloS one. 2017;12(8):e0181916.

13. van Netten JJ, Lazzarini PA, Armstrong DG, et al. Diabetic Foot Australia guideline on footwear for people with diabetes. Journal of Foot and Ankle Research. 2018;11(1):2.

14. Bus S, Valk G, Van Deursen R, et al. The effectiveness of footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in diabetes: a systematic review. Diabetes/metabolism research and reviews. 2008;24(S1):S162-S180.

15. Bus SA, Deursen RW, Armstrong DG, et al. Footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in patients with diabetes: a systematic review. Diabetes/Metabolism Research & Reviews. 2016;32:99-118 120p.

16. Heuch L, Streak Gomersall J. Effectiveness of offloading methods in preventing primary diabetic foot ulcers in adults with diabetes: a systematic review. JBI Database System Rev Implement Rep. 2016;14(7):236-265.

17. Paton J, Bruce G, Jones R, Stenhouse E. Effectiveness of insoles used for the prevention of ulceration in the neuropathic diabetic foot: a systematic review. Journal of Diabetes and its Complications. 2011;25(1):52-62.

18. van Netten JJ, Price PE, Lavery LA, et al. Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review. Diabetes/Metabolism Research And Reviews. 2016;32 Suppl 1:84-98.

19. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ (Clinical research ed). 2009;339:b2700.

20. Albert S, Rinoie C. Effect of custom orthotics on plantar pressure distribution in the pronated diabetic foot. The Journal of foot and ankle surgery : official publication of the American College of Foot and Ankle Surgeons. 1994;33(6):598-604.

21. Arts MLJ, Haart M, Waaijman R, et al. Data-driven directions for effective footwear provision for the high-risk diabetic foot. Diabetic Medicine. 2015;32(6):790-797 798p.

22. Arts MLJ, Waaijman R, de Haart M, Keukenkamp R, Nollet F, Bus SA. Offloading effect of therapeutic footwear in patients with diabetic neuropathy at high risk for plantar foot ulceration. Diabetic Medicine. 2012;29(12):1534-1541 1538p.

23. Barnett S. The clinical effectiveness of orthoses prescribed to control and reduce diabetic foot pathology. University of the West of England at Bristol (United Kingdom). 2002;http://hdl.handle.net/10068/598967.

24. Birke JA, Foto JG, Pfiefer LA. Effect of orthosis material hardness on walking pressure in high-risk diabetes patients. Journal of Prosthetics & Orthotics (JPO). 1999;11(2):43-46 44p.

25. Burns J, Wegener C, Begg L, Vicaretti M, Fletcher J. Randomized trial of custom orthoses and footwear on foot pain and plantar pressure in diabetic peripheral arterial disease. Diabetic Medicine. 2009;26(9):893-899 897p.

26. Bus SA, Haspels R, Busch-Westbroek TE. Evaluation and optimization of therapeutic footwear for neuropathic diabetic foot patients using in-shoe plantar pressure analysis. Diabetes care. 2011;34(7):1595-1600.

27. Bus SA, Ulbrecht JS, Cavanagh PR. Pressure relief and load redistribution by custom-made insoles in diabetic patients with neuropathy and foot deformity. Clinical biomechanics (Bristol, Avon). 2004;19(6):629-638.

28. Busch K, Chantelau E. Effectiveness of a new brand of stock ‘diabetic’shoes to protect against diabetic foot ulcer relapse. A prospective cohort study. Diabetic medicine. 2003;20(8):665-669.

29. Chantelau E, Kushner T, Spraul M. How effective is cushioned therapeutic footwear in protecting diabetic feet? A clinical study. Diabetic medicine : a journal of the British Diabetic Association. 1990;7(4):355-359.

30. Chapman JD, Preece S, Braunstein B, et al. Effect of rocker shoe design features on forefoot plantar pressures in people with and without diabetes. Clinical biomechanics (Bristol, Avon). 2013;28(6):679-685.

31. Colagiuri S, Marsden LL, Naidu V, Taylor L. The use of orthotic devices to correct plantar callus in people with diabetes. Diabetes Research And Clinical Practice. 1995;28(1):29-34.

32. Cumming A, Bayliff T. Plantar pressure: comparing two poron insoles. Diabetic Foot Journal. 2011;14(2):86-89 84p.

33. Donaghue VM, Sarnow MR, Giurini JM, Chrzan JS, Habershaw GM, Veves A. Longitudinal in-shoe foot pressure relief achieved by specially designed footwear in high risk diabetic patients. Diabetes research and clinical practice. 1996;31(1):109-114.

34. Fernandez MLG, Lozano RM, Diaz MIG-Q, Jurado MAG, Hernandez DM, Montesinos JVB. How effective is orthotic treatment in patients with recurrent diabetic foot ulcers? Journal of the American Podiatric Medical Association. 2013;103(4):281-290.

35. Frykberg RG, Bailey LF, Matz A, Panthel LA, Ruesch G. Offloading properties of a rocker insole. A preliminary study. Journal of the American Podiatric Medical Association. 2002;92(1):48-53.

36. Guldemond NA, Leffers P, Schaper NC, et al. The effects of insole configurations on forefoot plantar pressure and walking convenience in diabetic patients with neuropathic feet. Clinical Biomechanics. 2007;22(1):81-87.

37. Hastings MK, Mueller MJ, Pilgram TK, Lott DJ, Commean PK, Johnson JE. Effect of Metatarsal Pad Placement on Plantar Pressure in People with Diabetes Mellitus and Peripheral Neuropathy. FOOT AND ANKLE INTERNATIONAL. 2007;28(1):84.

38. Hellstrand Tang U, Zugner R, Lisovskaja V, Karlsson J, Hagberg K, Tranberg R. Comparison of plantar pressure in three types of insole given to patients with diabetes at risk of developing foot ulcers - A two-year, randomized trial. Journal of Clinical and Translational Endocrinology. 2014;1(4):121-132.

39. Hsi W, Chai H, Lai J. Comparison of pressure and time parameters in evaluating diabetic footwear. American Journal of Physical Medicine & Rehabilitation. 2002;81(11):822-829 828p.

40. Hsi W, Chai H, Lai J. Evaluation of rocker sole by pressure-time curves in insensate forefoot during gait. American Journal of Physical Medicine & Rehabilitation. 2004;83(7):500-506 507p.

41. Kastenbauer T, Sokol G, Auinger M, Irsigler K. Running shoes for relief of plantar pressure in diabetic patients. Diabetic Medicine. 1998;15(6):518-522.

42. Lavery LA, Lafontaine J, Higgins KR, Lanctot DR, Constantinides G. Shear-reducing insoles to prevent foot ulceration in high-risk diabetic patients. Advances in Skin & Wound Care. 2012;25(11):519-526.

43. Lin T-L, Sheen H-M, Chung C-T, et al. The effect of removing plugs and adding arch support to foam based insoles on plantar pressures in people with diabetic peripheral neuropathy. Journal Of Foot And Ankle Research. 2013;6(1):29-29.

44. Lobmann R, Kayser R, Kasten G, et al. Effects of preventative footwear on foot pressure as determined by pedobarography in diabetic patients: a prospective study. Diabetic medicine. 2001;18(4):314-319.

45. Lott DJ, Hastings MK, Commean PK, Smith KE, Mueller MJ. Effect of footwear and orthotic devices on stress reduction and soft tissue strain of the neuropathic foot. Clinical biomechanics. 2007;22(3):352-359.

46. Mohamed O, Cerny K, Rojek L, Herbert K, Turner R, Waistell S. The Effects of Plastazote(R) and Aliplast(R)/Plastazote(R) Orthoses on Plantar pressures in Elderly Persons With Diabetic Neuropathy. JOURNAL OF PROSTHETICS AND ORTHOTICS. 2004;16(2):55.

47. Mueller MJ, Lott DJ, Hastings MK, Commean PK, Smith KE, Pilgram TK. Efficacy and mechanism of orthotic devices to unload metatarsal heads in people with diabetes and a history of plantar ulcers. Physical Therapy. 2006;86(6):833-842.

48. Owings TM, Woerner JL, Frampton JD, Cavanagh PR, Botek G. Custom therapeutic insoles based on both foot shape and plantar pressure

measurement provide enhanced pressure relief. Diabetes care. 2008;31(5):839-844.

49. Paton JS, Stenhouse E, Bruce G, Jones R. A longitudinal investigation into the functional and physical durability of insoles used for the preventive management of neuropathic diabetic feet. Journal of the American Podiatric Medical Association. 2014;104(1):50-57.

50. Paton JS, Stenhouse EA, Bruce G, Zahra D, Jones RB. A comparison of customised and prefabricated insoles to reduce risk factors for neuropathic diabetic foot ulceration: a participant-blinded randomised controlled trial. Journal Of Foot And Ankle Research. 2012;5(1):31-31.

51. Perry JE, Ulbrecth JS, Derr JA, Cavanagh PR. The use of running shoes to reduce plantar pressures in patients who have diabetes. Journal of Bone and Joint Surgery - Series A. 1995;77(12):1819-1828.

52. Praet SFE, Louwerens JWK. The influence of shoe design on plantar pressures in neuropathic feet. Diabetes care. 2003;26(2):441-445.

53. Raspovic A, Newcombe L, Lloyd J, Dalton E. Effect of customized insoles on vertical plantar pressures in sites of previous neuropathic ulceration in the diabetic foot. The Foot. 2000;10(3):133-138.

54. Reiber GE, Smith DG, Boone DA, et al. Design and pilot testing of the DVA/Seattle Footwear System for diabetic patients with foot insensitivity. Journal of rehabilitation research and development. 1997;34(1):1.

55. Reiber GE, Smith DG, Wallace C, et al. Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized controlled trial. Jama. 2002;287(19):2552-2558.

56. Rizzo L, Tedeschi A, Fallani E, et al. Custom-made orthesis and shoes in a structured follow-up program reduces the incidence of neuropathic ulcers in high-risk diabetic foot patients. The international journal of lower extremity wounds. 2012;11(1):59-64.

57. Sacco IC, Akashi PM, Hennig EM. A comparison of lower limb EMG and ground reaction forces between barefoot and shod gait in participants with diabetic neuropathic and healthy controls. BMC musculoskeletal disorders. 2010;11:24-24 21p.

58. Scherer PR. A clinical study to determine the effects of wearing Earth Shoes. Journal Of The American Podiatry Association. 1975;65(5):422-443.

59. Soulier SM. The use of running shoes in the prevention of plantar diabetic ulcers. Journal of the American Podiatric Medical Association. 1986;76(7):395-400.

60. Tsung BYS, Zhang M, Mak AFT, Wong MWN. Effectiveness of insoles on plantar pressure redistribution. Journal Of Rehabilitation Research And Development. 2004;41(6A):767-774.

61. Uccioli L, Faglia E, Monticone G, et al. Manufactured shoes in the prevention of diabetic foot ulcers. Diabetes care. 1995;18(10):1376-1378.

62. Ulbrecht JS, Hurley T, Mauger DT, Cavanagh PR. Prevention of recurrent foot ulcers with plantar pressure–based in-shoe orthoses: the CareFUL prevention multicenter randomized controlled trial. Diabetes care. 2014;37(7):1982-1989.

63. Viswanathan V, Madhavan S, Gnanasundaram S, et al. Effectiveness of Different Types of Footwear Insoles for the Diabetic Neuropathic Foot: A follow-up study. Diabetes care. 2004;27(2):474-477.

64. Waaijman R, Arts MLJ, Haspels R, Busch-Westbroek TE, Nollet F, Bus SA. Pressure-reduction and preservation in custom-made footwear of patients with diabetes and a history of plantar ulceration. Diabetic Medicine. 2012;29(12):1542-1549 1548p.

65. Wrobel J, Ammanath P, Le T, et al. A novel shear-reduction insole effect on thermal response to walking stress, balance, and gait. Diabetes. 2014;63:A57.

66. Nouman M, Leelasamran W, Chatpun S. Effectiveness of Total Contact Orthosis for Plantar Pressure Redistribution in Neuropathic Diabetic Patients During Different Walking Activities. Foot & ankle international / American Orthopaedic Foot and Ankle Society [and] Swiss Foot and Ankle Society. 2017;38(8):901-908.

67. Preece SJ, Chapman JD, Braunstein B, Bruggemann GP, Nester CJ. Optimisation of rocker sole footwear for prevention of first plantar ulcer: comparison of group-optimised and individually-selected footwear designs. J Foot Ankle Res. 2017;10:27.

68. Telfer S, Woodburn J, Collier A, Cavanagh PR. Virtually optimized insoles for offloading the diabetic foot: A randomized crossover study. J Biomech. 2017;60:157-161.

69. Abbott CA, Chatwin KE, Hasan ANB, et al. Novel plantar pressure-sensing smart insoles reduce foot ulcer incidence in 'high-risk' diabetic patients: A longitudinal study. Diabetologia. 2018;61.

70. Lopez-Moral M, Lazaro-Martinez JL, Garcia-Morales E, Garcia-Alvarez Y, JavierAlvaro-Afonso F, Molines-Barroso RJ. Clinical efficacy of therapeutic footwear with a rigid rocker sole in the prevention of recurrence in patients with diabetes mellitus and diabetic polineuropathy: A randomized clinical trial. PloS one. 2019;14(7).

71. Martinez-Santos A, Preece S, Nester CJ. Evaluation of orthotic insoles for people with diabetes who are at-risk of first ulceration. Journal of foot and ankle research. 2019;12:35.

72. Nouman M, Dissaneewate T, Leelasamran W, Chatpun S. The insole materials influence the plantar pressure distributions in diabetic foot with neuropathy during different walking activities. Gait & posture. 2019;74:154-161.

73. Parker DJ, Martinez-Santos A, Nester C, et al. A randomised controlled trial and cost-consequence analysis of traditional and digital foot orthoses supply chains in a National Health Service setting: application to feet at risk of diabetic plantar ulceration. Journal of foot and ankle research. 2019;12:2.

74. Institute TJB. Joanna Briggs Institute Reviewers' Manual: 2014 Edition. Joanna Briggs Institute Adelaide; 2014.

75. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed). 2003;327(7414):557-560.

76. Institute JB. Joanna Briggs Institute reviewers' manual: 2017 edition [Internet]. Australia: Joanna Briggs Institute; 2017 [cited 2018 September 18].

77. Abbott CA, Chatwin KE, Foden P, et al. Innovative intelligent insole system reduces diabetic foot ulcer recurrence at plantar sites: a prospective, randomised, proof-of-concept study. The Lancet Digital Health. 2019;1(6):e308-e318.

78. Bus SA, Ulbrecht JS, Cavanagh PR. Pressure relief and load redistribution by custom-made insoles in diabetic patients with neuropathy and foot deformity. Clinical Biomechanics. 2004;19(6):629-638.

79. San Tsung BY, Zhang M, Mak AFT, Wong MWN. Effectiveness of insoles on plantar pressure redistribution. Journal of rehabilitation research and development. 2004;41(6A):767.

80. Chen WP, Ju CW, Tang FT. Effects of total contact insoles on the plantar stress redistribution: a finite element analysis. Clinical biomechanics (Bristol, Avon). 2003;18(6):S17-24.

81. Patry J, Belley R, Cote M, Chateau-Degat ML. Plantar pressures, plantar forces, and their influence on the pathogenesis of diabetic foot ulcers: a review. Journal of the American Podiatric Medical Association. 2013;103(4):322-332.

82. Nawoczenski DA, Birke JA, Coleman WC. Effect of rocker sole design on plantar forefoot pressures. Journal of the American Podiatric Medical Association. 1988;78(9):455-460.

83. Schaff PS, Cavanagh PR. Shoes for the insensitive foot: the effect of a "rocker bottom" shoe modification on plantar pressure distribution. Foot Ankle. 1990;11(3):129-140.

84. Jeffcoate WJ, Bus SA, Game FL, et al. Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. The lancet Diabetes & endocrinology. 2016;4(9):781-788.

85. Rome K. A study of the properties of materials used in podiatry. Journal of the American Podiatric Medical Association. 1991;81(2):73-83.

86. Brodsky JW, Pollo FE, Cheleuitte D, Baum BS. Physical properties, durability, and energy-dissipation function of dual-density orthotic materials used in insoles for diabetic patients. Foot & ankle international / American Orthopaedic Foot and Ankle Society [and] Swiss Foot and Ankle Society. 2007;28(8):880-889.

87. Paton J, Jones RB, Stenhouse E, Bruce G. The physical characteristics of materials used in the manufacture of orthoses for patients with diabetes. Foot & ankle international / American Orthopaedic Foot and Ankle Society [and] Swiss Foot and Ankle Society. 2007;28(10):1057-1063.

2.14 Electronic supplementary material

Electronic supplementary material 1 – Example of search string

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fedm2.132&file=edm2132-sup-0001-AppendixS1.docx

Electronic supplementary material 2 – Appraisal of studies

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fedm2.132&file=edm2132-sup-0002-AppendixS2.docx

Electronic supplementary material 3 – Profile of insole

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fedm2.132&file=edm2132-sup-0003-AppendixS3.docx

Electronic supplementary material 4 – Rocker profile

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fedm2.132&file=edm2132-sup-0004-AppendixS4.docx

Electronic supplementary material 5 – Modifications to footwear

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fedm2.132&file=edm2132-sup-0005-AppendixS5.docx

Electronic supplementary material 6 – Metatarsal modifications

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fedm2.132&file=edm2132-sup-0006-AppendixS6.docx

Electronic supplementary material 7 – Cut-out or aperture modifications

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fedm2.132&file=edm2132-sup-0007-AppendixS7.docx

Electronic supplementary material 8 – Casting technique

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fedm2.132&file=edm2132-sup-0008-AppendixS8.docx

Electronic supplementary material 9 – Fabrication informed by kinetic parameters

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fedm2.132&file=edm2132-sup-0009-AppendixS9.docx

Electronic supplementary material 10 – Materials of footwear and insoles

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fedm2.132&file=edm2132-sup-0010-AppendixS10.docx

Chapter 3 Development of the optimised insole

The development stage of the MRC's developing and evaluating complex interventions framework provides a contextual structure for developing an intervention prior to formal pilot testing (Craig *et al.*, 2008; Duncan *et al.*, 2020; Hoddinott, 2015; O'Cathain *et al.*, 2019). Using evidence from the previous chapter on the design features of footwear and insoles to offload the feet of people with diabetes and DPN, this chapter describes how the novel optimised insole intervention was developed. It summarises the proof-of-concept for designing and modifying an insole by in-shoe plantar pressure analysis to reduce the risk of DFU and how this influenced the development of an algorithm to guide the design of the optimised insole. The theoretical construct of the optimised insole intervention is described, culminating with the optimised insole algorithm and the novel thought in its application.

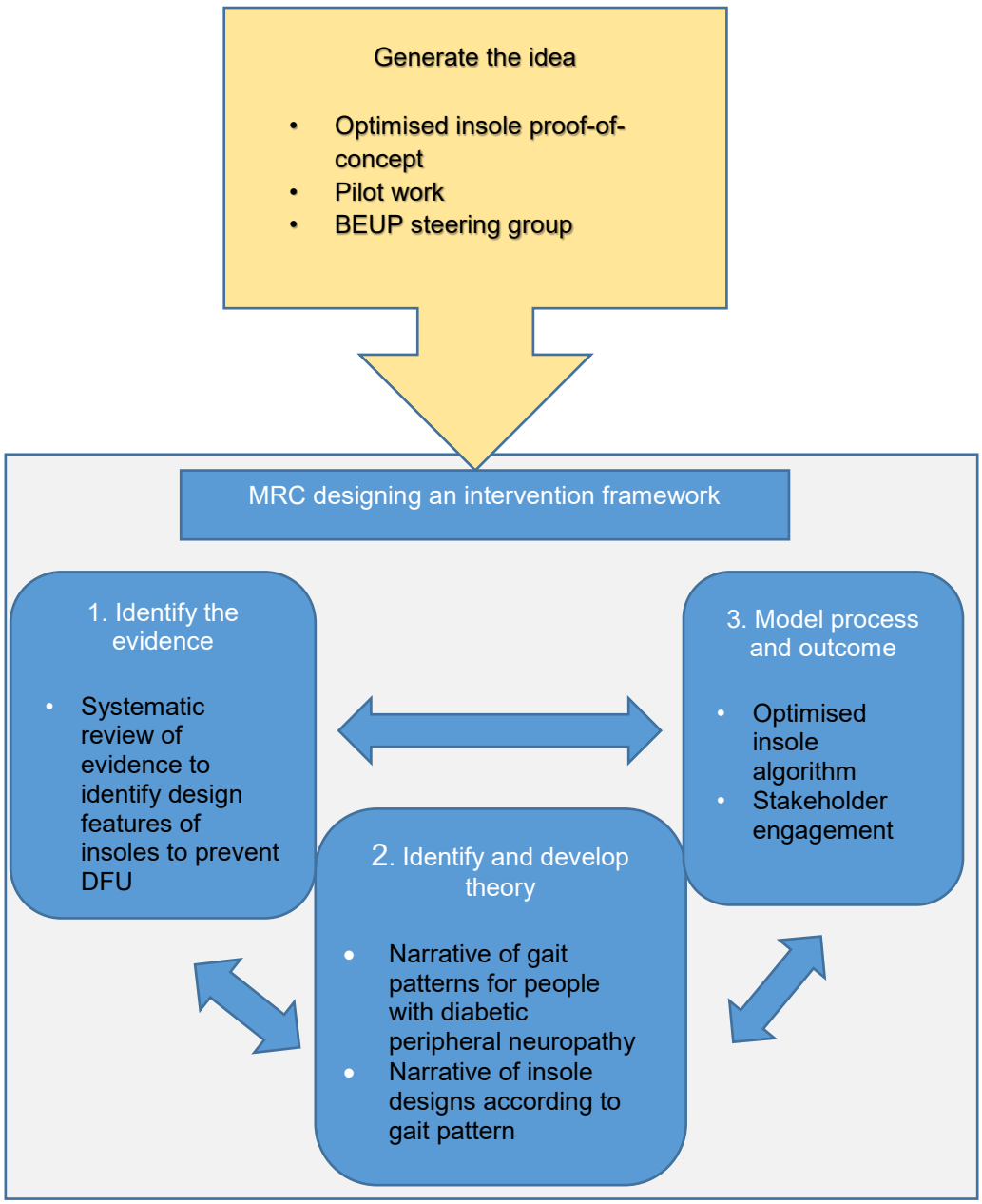
3.1 Optimising insoles - Proof-of-concept

The proof-of-concept for optimising insoles to reduce the risk of DFU was established before commencing my PhD journey. In 2014, lay members, NHS clinicians and researchers of the Balance and Ulcer Prevention Team (BEUP) steering group discussed the concept of using in-shoe plantar pressure measures to guide the design and modification of insoles. Resultantly, pilot work was undertaken to investigate the proof-of-concept of designing an insole informed by in-shoe pressure analysis (REC reference: 13/SW/0310, 13 June 2014, IRAS project ID. 138428, Unpublished). The intention was to determine whether the recommendations from the pilot study adequately addressed the key concerns about the insole and the delays experienced in its provision. A

personalised approach to footwear and insole design for each patient is desirable, but such an approach is not always clinically practical (van Netten *et al.*, 2020a). It also hoped to gain an indication of the likely enthusiasm and willingness of participants to be involved in future research within this area and to gather specific comments on some aspects of the proposed trial methodology. An important issue, however, that was not addressed by this pilot work was the predicament of variability amongst participants in plantar pressure reduction. These findings guided the work to develop the optimised insole.

3.2 Development of the optimised insole

Building on the proof-of-concept findings, the optimised insole was developed as part of the PhD journey. As acknowledged by the developers of the MRC Framework (Craig *et al.*, 2013) and other commentators (O'Cathain *et al.*, 2019), while the process of developing and evaluating a complex intervention has several phases, these may not follow a linear sequence. This was the reality of developing the optimised insole, which followed a more dynamic and iterative approach. Interchanging between the three-phases outlined in the development phase of the MRC framework enabled iterations and refinements to inform the development of the optimised insole (Figure 3.1). The impact of iterations compelled a constant review of the evidence and revisions of the theoretical underpinning and modelling phases. However, for ease of understanding for the reader, this next section will describe the development of the optimised insole linearly with the identification of evidence as the first step.



BEUP-Balance enhancement and ulcer prevention, MRC- Medical Research Council, DFU-diabetic foot ulceration

Figure 3.1 Pathway of the optimised insole development

The notion of the optimised insole stemmed from the idea that a single footwear or insole design cannot successfully decrease peak plantar pressures for people with DPN. One RCT showed that the effectiveness of a custom-made and prefabricated insole in reducing peak pressure was inconsistent amongst

participants with DPN (Paton *et al.*, 2012). It demonstrated that insoles' ability to reduce load under the foot is highly variable, difficult to predict, and does not guarantee a clinically significant improvement.

Therefore, one intention of the optimised insole is to reduce the variability in load reduction using real-time pressure analysis to inform the design and modification of the insole. Kinetic parameters, such as the temporal profile and magnitude of load pattern on the plantar foot, could provide insights into the underlying changes in walking patterns and quantitative observation of gait (Raja, Neptune & Kautz, 2012). Temporal profiles can be determined by force-time curve analysis and magnitude profiles by peak pressure-time analysis.

This approach to insole design differs from the traditional paradigms of insole action, which advocate the ‘correction of foot function’ (Dananberg, 2000; Fuller, 1999; Kirby, 2001; McPoil & Hunt, 1995; Root, 1973). Other approaches highlight a neuromuscular interaction (Nigg, Nurse & Stefanyshyn, 1999) and a preferred movement path and comfort filter (Nigg *et al.*, 2015). Nonetheless, these paradigms were not developed or evaluated in populations with DPN, although they are used to guide insole and footwear design and modification in clinical practice.

After recognising the potential for using temporal and magnitude loading profiles as an approach to guide the design and modification of insoles for people with DPN, further exploration of the concept was initiated. The exploration aligned with the optimised insole proof-of-concept and used the MRC framework for developing and evaluating complex interventions to develop the optimised insole algorithm.

3.2.1 Identifying the evidence - Implications of the systematic review

The first step of the MRC framework identifies the evidence about similar interventions and the methods used to evaluate them. In the absence of relevant, timely, high-quality systematic reviews, it is advised to conduct one and update as evaluation proceeds.

Recognising which insole and footwear design feature effectively reduced plantar pressures in people with DPN was a key component of the optimising insole. Accordingly, a systematic review of the literature was conducted to inform its design, reported in Chapter two. The development of the systematic review ran parallel with the formulation of the optimised insole algorithm and the feasibility study. The initial results informed the algorithm, and was subsequently supported by the narrative of the added later studies, as none were appropriate for inclusion in the meta-analyses.

Within the included studies, few studies justified the mechanism by which the footwear and insoles were designed and modified. No studies designed and modified footwear and insoles using temporal profiles. Accordingly, the review highlighted the difficulty in differentiating the effect of the different insole and footwear features in reducing the risk of DFU in those with DPN. Providing evidence to support the standardisation of footwear and insoles in reducing the risk of DFU in people with DPN will significantly improve the quality and support of the broader evidence base.

Having established a gap in the evidence in using temporal profiles to design and modify footwear and insoles for people with DPN, the next step in the MRC framework when developing an intervention is to identify/generate theory.

3.2.2 Identifying/developing theory

Having critically evaluated the literature, this section moves on to present the theoretical underpinning of the development of the optimised insole algorithm for reducing the risk of DFU in people with DPN. It introduces the concept that there are different walking gait patterns for people with DPN compared to those without DPN. More importantly, it describes the different walking gait patterns amongst the DPN population, and that these differences are attributable to pathophysiological changes with DPN. It is hypothesised that changes in gait patterns will infer different load timing and pressure profiles of the feet, which can be used to classify three categories of gait style. This application of gait type for insole provision in people with DPN is novel. Clinical observation and experience has indicated that the three distinct walking gait load timing and pressure profile styles have shown to necessitate insoles with different design features based on the timing and location of their application. This reasoning was used to inform the optimised insole algorithm.

3.2.2.1 Walking gait characteristics and diabetic peripheral neuropathy

It is well established that elevated MPPP as a risk factor for DFU is more significant in patients with DPN. For example, Mueller et al. (2008) indicated that the MPPP in the forefoot was 34% greater in the DPN group than in the DM control group (Mueller *et al.*, 2008). One of the many determinants of elevated MPPP under the foot is gait characteristics. Based on gait recognition tools and plantar pressure imaging, dynamic foot pressure patterns can reflect walking gait patterns (Wafai *et al.*, 2015). One experimental study reported high classification rates of foot pressure and gait biometrics in an unshod walking,

healthy population (Pataky *et al.*, 2012). Other experimental studies involving healthy participants have reported linear relationships between walking speed, foot posture and peak pressures in the plantar foot, although variations existed amongst the distribution in different foot regions (Buldt *et al.*, 2018; Warren, Maher & Higbie, 2004).

In those with DPN, it is recognised that walking gait characteristics are attributed to the pathophysiological changes associated with diabetes, which contributes to elevated MPPP (Giacomozzi *et al.*, 2002; Mueller *et al.*, 1994). The two most recent systematic reviews have reported significant differences in biomechanical gait characteristics for people with DPN compared to healthy control participants and people with DM and without DPN (Fernando *et al.*, 2013; Hazari *et al.*, 2016). Fernando et al. (2013) included 16 studies reporting that only plantar pressures and stance time differ significantly in DPN participants compared with participants without DPN and healthy controls. Hazari et al.'s (2016) review and meta-analyses included 25 studies but omitted previous DFU as a criterion and focused on barefoot walking. They reported slower gait velocity, shorter stride length, higher stance times, variation in kinematic variables of the hip, knee and ankle and higher plantar pressures. Both systematic reviews reported the limitations of their findings due to the high levels of heterogeneity and inconsistency among the included studies, and both omitted any intra-population variations in gait characteristics for participants with DPN.

It is believed that there are further gait changes due to the progressive decline in pathophysiological changes associated with DPN. One cross-sectional study

compared small groups of healthy controls to those with DM, those with DPN and those with DPN and history of DFU, using the complication of a diabetic foot ulcer as a symptom of worsening DPN (Raspovic, 2013). They reported significant differences in foot and ankle functionality and gait alterations in those with a history of DFU compared to the cohort without a history of DFU. Another study reported slower gait speed and reduced knee flexion in those with a history of DFU than those without this history (Katoulis *et al.*, 1997). A longitudinal study over 12-months compared a cohort of participants with a non-healing plantar diabetic foot ulcer with those without a history of DFU (Fernando *et al.*, 2019). They reported further gait changes of slower walking speed, smaller step length and abducted foot progression angle in those with the diabetic foot ulcer, although they could not conclusively rule out gait changes due to the presence of the diabetic foot ulcer.

Despite clear evidence of changes in the gait characteristics of people with DPN, and according to the severity of DPN, few studies have evaluated the relationship with the timing of plantar loading patterns. One study established four distinct loading patterns using regional pressure impulses in the forefoot of persons with DM, including those with a history of DFU (Deschamps *et al.*, 2013). However, the timing of the loading and intra-participant characteristics to determine the severity of disease was not reported. Another observational study correlated pressure-time curves with functional impairments of walking gait associated with DPN severity (Giacomozzi & Martelli, 2006). The authors analysed the gait characteristics of 97 people with mild to severe DPN and reported that walking gait events' timing were associated with elevated pressures. They were also able to classify the shape and amplitude of the

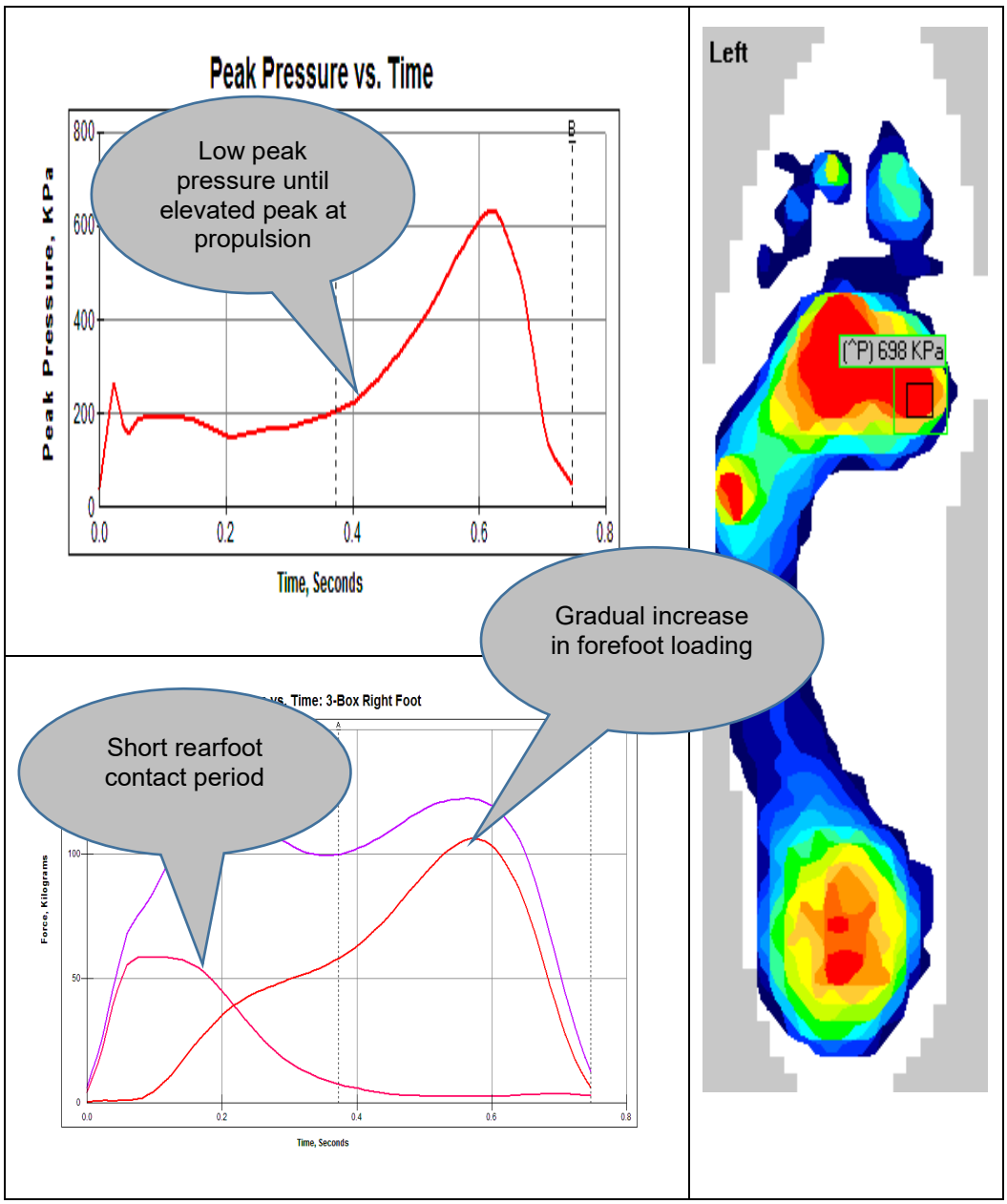
pressure-time curve to form three distinct clusters, although a link with DFU was not established. Interestingly, there was no association with changes in the magnitude of plantar pressure and worsening DPN-related changes in gait characteristics. This could be attributed to compensatory gait strategies employed that, for some, do not increase plantar pressures.

Using a similar approach to identify and cluster groups of patients, a novel approach, developed on the basis of observations/measurements undertaken during my clinical practice and the practice of other members of the BEUP team, proposes that there are three different patterns of walking gait for people with DPN. These walking gait patterns appear to relate to the severity of DPN changes with a difference in plantar pressure and load timing patterns. The three profiles are: '*Propulsing gait', 'Stomping gait', and 'Variable gait'*. These are classified according to the pressure-time curve and the difference between the two peaks of the vertical component of ground reaction force (VGRF) during the stance phase. VGRF is obtained by collecting successive maximum values of plantar pressure during the whole stance phase of gait (Giacomozzi & Martelli, 2006). The VGRF can also distinguish normal from pathological gait patterns (Horst, Mildner & Schöllhorn, 2017). For example, one meta-analysis reported a VGRF reduction in both the loading and propulsion phases for older adults in walking compared to younger participants (Boyer *et al.*, 2017). Other studies have used the magnitude and timing of the VGRF peaks to assess treatment effects following ACL reconstruction (Pietrosimone *et al.*, 2019) and gait retraining in healthy individuals (Schenck & Kesar, 2017).

3.2.2.1.1 ‘Propulsing gait’ pattern

The ‘propulsing gait’ pattern is observed with an early heel lift leading to a prolonged forefoot loading period culminating in a late burst at the push-off phase. This is illustrated by force-time graphs indicating shorter heel contact and longer forefoot periods in the stance phase (Figure 3.2). Based on unpublished observations, pressure analysis typically shows a peak pressure-time curve that builds over stance to form a short, elevated peak at propulsion.

Individuals displaying a ‘propulsing gait’ pattern typically are thought to have more moderate pathophysiological changes as a consequence of DPN. They are believed to demonstrate a preference for using an ankle strategy where the body rotates about the ankle joint during gait due to the reduced ankle and midfoot joint sagittal plane mobility (Jeong *et al.*, 2021). This is associated with an early heel lift culminating in a push-off strategy (Petrovic *et al.*, 2017), considered more efficient for propulsion with a bouncing gait with the body’s Centre-Of-Mass (COM) increasing in speed (Zelik & Adamczyk, 2016).



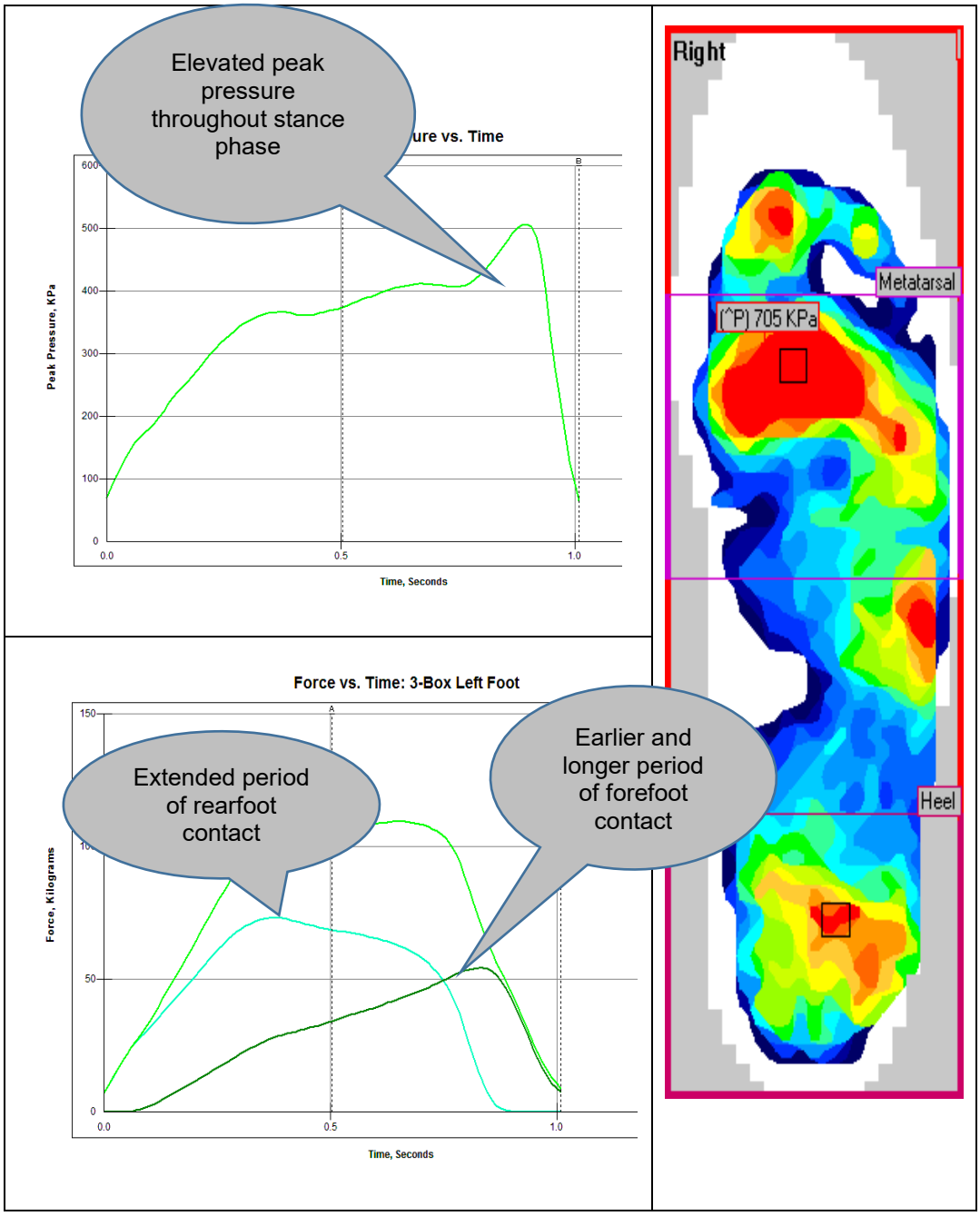
Top left graph shows the pressure-time curve for the stance phase of walking gait with an elevated forefoot plantar pressure at late stance. Bottom left graph shows the force-time of the stance phase of gait with purple representing the overall force-time stance phase, pink representing a short rearfoot contact period (early heel lift) and red representing forefoot contact period (early forefoot loading). The figure on the right shows the 2D representation of an in-shoe plantar pressure distribution with the box showing the region of interest, ^P-mean peak plantar pressure for region of interest, red –areas of high plantar pressure, yellow- areas of moderate plantar pressure, blue-areas of least plantar pressure

Figure 3.2 Pressure-time and force-time curves illustrative of a "propulsing" gait pattern

3.2.2.1.2 ‘Stomping gait’ pattern

The observation of a ‘stomping gait’ pattern exhibits with the forefoot and rearfoot in contact with the floor for a high proportion of the stance phase. This is illustrated by force-time curves showing prolonged periods of both forefoot and rearfoot over the entire contact phase (Figure 3.3). Based on unpublished observations, pressure analysis typically shows an early and prolonged peak in the peak-pressure time curve (Figure 3.3). The ‘stomping gait’ pattern is identified by a slower gait velocity, shorter step length and increased double support time.

Resultantly, individuals displaying a ‘stomping gait’ pattern hypothetically have reduced ankle and metatarsal phalangeal joint dorsiflexion in gait associated with the pathophysiological progression of DPN. Decreases in sub-talar joint ROM (Sinacore *et al.*, 2013) and a reduced ROM of the first metatarsal phalangeal joint is a determining factor for hallux pressures during midstance and propulsion for those with DPN (Payne, Turner & Miller, 2002). Concurrent conditions, such as high BMI (Tabue-Teguo *et al.*, 2020) and frailty (Tuttle *et al.*, 2018), will slow gait speed characteristics. A delayed heel lift and lack of rocker in the midstance and propulsive phases are associated with weakness in the plantar-flexor muscles and reduced proprioception from the sensory neuropathy (Savelberg *et al.*, 2009). Changes are seen in the shift of the loading pattern from the rearfoot to the anterior part of the foot, which are responsible for the forward propulsion during the push-off phase (Bacarin, Sacco & Hennig, 2009). The stomping pattern is assumed to be a safer and more stable walking gait (Franz, 2016).

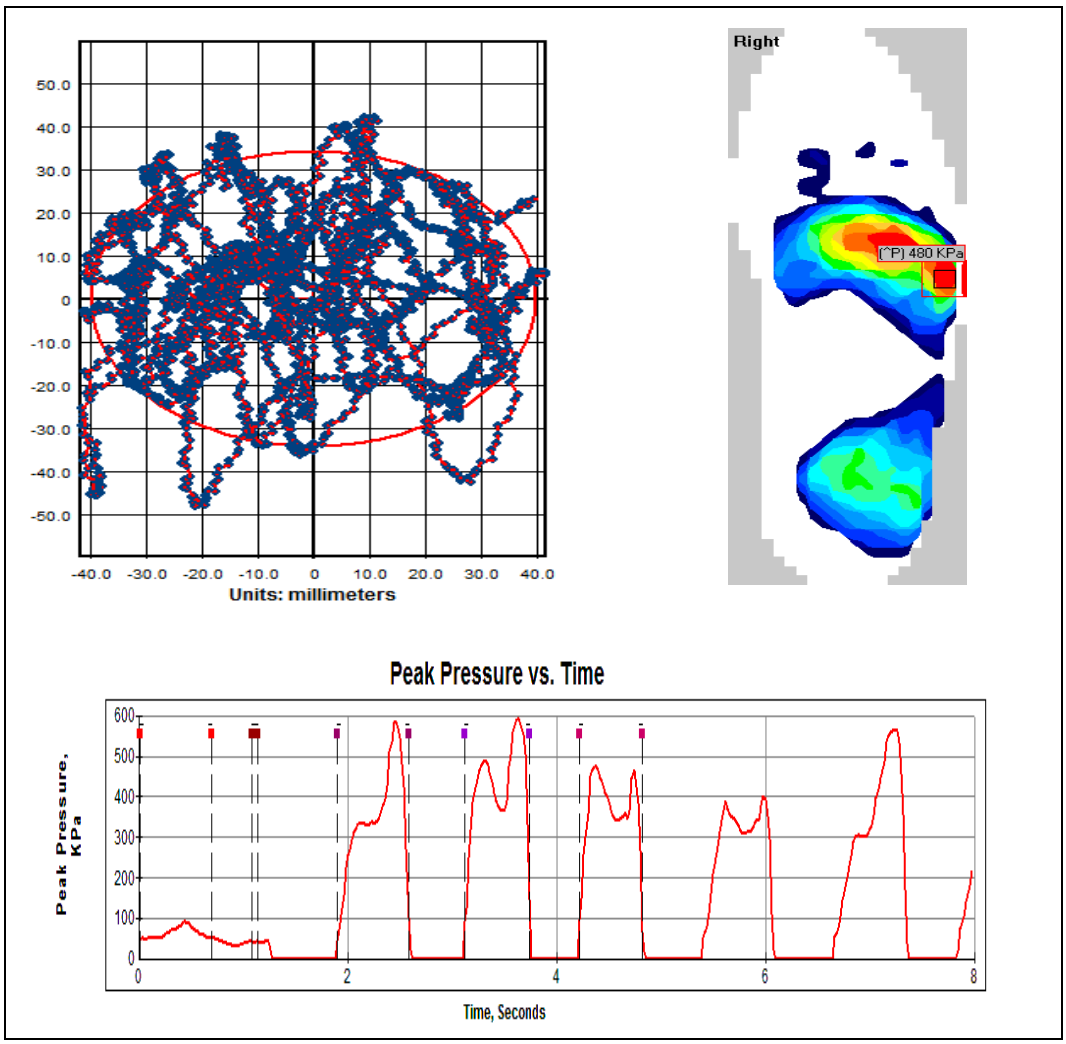


Top left graph shows the pressure-time curve for the stance phase of walking gait with a loss of 1st and 3rd rocker. Bottom left graph shows the force-time of the stance phase of gait with light green representing the overall force-time stance phase with an increased mid-stance period with both forefoot and rearfoot in floor contact; blue line represents the increased rearfoot contact period and dark green represents forefoot contact period. The figure on the right shows the 2D representation of an in-shoe plantar pressure distribution with the box showing the region of interest, ^P-mean peak plantar pressure for region of interest, red –areas of high plantar pressure, yellow- areas of moderate plantar pressure, blue-areas of least plantar pressure

Figure 3.3 Pressure-time and force-time curves illustrative of a "stomping" gait pattern

3.2.2.1.3 ‘Variable gait’ pattern

Observations of the ‘variable gait’ pattern identify with a fluctuating centre-of-mass excursion with increased step-to-step variability (Figure 3.3). Based on unpublished observations, step-by-step variations of a slower gait velocity, and an unstable ataxic gait are frequently seen, often with variations in step width and length. This pattern is thought to identify with increased severity of DPN. These patients struggle to balance with confidence and find difficulty performing balance tasks (Mustapa *et al.*, 2016). There is excessive anterior-posterior postural sway in people with DPN, both with eyes open and shut conditions. The possible presence of neuropathic pain due to the progression of DPN, will increase step-to-step variability (Lalli *et al.*, 2013). The impact of the DPN impairs sensorimotor function, balance, mobility with an associated increase in risk and fear of falling, compared to those without DPN and healthy controls (D'Silva *et al.*, 2016; Wettasinghe *et al.*, 2020). Individuals with this pattern type are likely to report a history of frequent falls (Dingwell & Cavanagh, 2001).



Top left graph shows the centre-of-mass movement in the anterior-posterior and lateral-medial directions in stance phase. The figure on the right shows the 2D representation of an in-shoe plantar pressure distribution with the box showing the region of interest, ^P-mean peak plantar pressure for region of interest, red –areas of high plantar pressure, yellow- areas of moderate plantar pressure, blue-areas of least plantar pressure. Bottom graph shows the irregularity of the peak pressure-time curves by each step.

Figure 3.4 Centre-of-pressure variability illustrative of a "variable" gait pattern

3.2.2.2 Insole design using force-time and plantar pressure analysis

Having established that walking gait differs amongst people with DPN, it is proposed that different insole designs and features are likely required according to the temporal load profile of each gait style. The insole design utilises principles that apply mechanical forces on various parts of the foot, at different times of the gait cycle to achieve the desired change and effect. Consequently,

the effectiveness of insoles in reducing plantar pressure must depend on the timing and point of its application on the foot during walking gait. It is proposed that different insole design features to reduce plantar pressure are required for different temporal load patterns (gait patterns) for people with DPN.

Insole materials were selected for their widespread use in current clinical practice. The prefabricated insole (Slimflex Full-length Medium Density (Shore A50), Algeos, UK) acted as a pre-constructed base to conform to concavo-convex contours of the foot. Specific insole features of metatarsal bar, arch profile and apertures were derived from findings from the systematic review (Collings *et al.*, 2020). Modifying the insole using real-time pressure data from the in-shoe system informed the appropriate placement of insole features, as well as providing confidence that the plantar pressure had been reduced. Other studies have successfully used modifications to guide the design of therapeutic footwear and insoles. Bus et al. (2011) reported an average of 1.6 rounds of modifications to optimise the footwear, with up to three rounds of modifications to reduce MPP below 200 kPa or 25% from baseline for regions of interest over 200kPa permitted (Bus, Haspels & Busch-Westbroek, 2011). However, large variations of 17.1% to 51.8% in peak pressure reduction occurred across the participant group, which could be attributed to the self-selection of footwear and insole modifications by the shoe technicians rather than following a prescribed pathway.

3.2.2.2.1 ‘Propulsing gait’ pattern insole

The ‘propulsing gait’ insole aims to reduce peak pressure at the regions of interest (ROI)’s by delaying heel lift and centre-of-pressure progression and

reducing the elevated peak pressure in the prolonged terminal stance phase (Table 3.1). The ‘propulsing gait’ pattern denotes that when the pressure is maximally elevated and ulcer risk potentially greatest, the insole action should correspond with when the insole is in contact with the ground. It is postulated that the traditional approach to insole design may not be best for a ‘propulsive gait’ because the increased total contact area is implemented at heel strike to mid-foot loading. With a ‘propulsing gait’ pattern, peak pressures are highest, and the risk of ulceration potentially greatest when the heel has left the floor and the total contact area of the insole is rendered ineffective. Thus, a different design is needed that will function during forefoot loading.

The provision of an arch profile insole with a cushioned top cover, cut out at the ROI(s) has shown to reduce direct pressure on the targeted site. The addition of a heel lift aims to reduce the time of forefoot loading and period spent on the elevated pressure area of the forefoot. One study showed a 27% reduction in forefoot pressure by increasing dorsiflexion range of motion and allowing the tibia to progress more quickly over the foot during stance with an Achilles lengthening procedure (Armstrong *et al.*, 1999). If required, adding a pad anterior to the ROI(s) and a rocker bar may prove beneficial by increasing the surface area and modifying the peak pressure timing away from the ROI (s).

Table 3.1 Insole design features for alternative walking gait patterns

Patient gait type	Insole design	Insole modifications Round 1	Insole modifications Round 2
'Propulsing gait' Aim – to reduce peak pressure by delaying heel lift and Centre of Pressure progression and modify abnormal loading patterns in terminal stance phase	• Issue a slimflex insole • Accommodate deformity/regions of interest with a dell/cut out • Add a 3mm poron heel cushion • Addition of 3mm poron medium density top-cover	• Addition of 3mm poron apron anterior to the region of interest	• Addition of 3mm EVA forefoot rocker
'Stomping gait' Aim- To reduce peak pressure by increasing the total contact area throughout the stance phase of gait	• Issue a slimflex insole • Accommodate deformity/regions of interest with a dell/cut out • Addition of 3mm poron medium density top-cover	• Addition of metatarsal pad to insole base	• Increase arch height/profile with 3mm poron • Addition of 3mm poron apron anterior to the region of interest
'Variable gait' Aim – to reduce peak pressures and minimise instability throughout the stance phase of gait	• Issue a 3mm base insole • Accommodate deformity/regions of interest with a dell/cut out • Addition of 3mm poron medium density top-cover	• Introduce metatarsal bar to insole base	• Increase the size of metatarsal bar proximally to medial longitudinal arch

ROI-Regions of interest; mm-millimetres, MPPP – Mean peak plantar pressure, EVA- Ethylene-vinyl acetate, kPa-kilopascal

3.2.2.2.2 'Stomping gait' pattern insole

The 'stomping gait' insole aims to reduce peak pressure at the ROI's by increasing total contact area throughout the stance phase of gait (Table 3.1), which is directionally proportional to reducing peak pressure

(Bus, Ulbrecht & Cavanagh, 2004; Tsung *et al.*, 2004). This gait pattern denotes that the whole foot is in contact with the floor throughout the stance phase. Therefore, increasing the amount of time the foot is in contact with the insole by way of a total contact insole aims to reduce pressure. Total contact insole is the traditionally accepted approach to insole design for reducing pressure for people with DPN.

The provision of an insole with an arch and top cover insole aims to increase the total contact area during the stance phase. The insertion of the cut-out under the ROI aims to reduce direct pressure at this site. If required, further modifications involving placement of a metatarsal pad, followed by increasing height of the arch profile and introduction of an apron anterior to the ROI, aims to increase surface contact area and increase the depth to the cut-out reducing direct pressure further.

3.2.2.2.3 'Variable gait' pattern insole

The 'variable gait' insole aims to reduce peak pressures and minimise instability throughout the stance phase of gait (Table 3.1). Previous work has shown that in people with diabetes and DPN, the addition of an insole with an arch profile increases sway and perception of instability, particularly in the anterior-posterior direction when compared to an insole without arch profile support (Paton *et al.*, 2016). The insole provided for this gait pattern group will correspondingly have a flat base with a cushioned top cover and a cut out at the ROI(s). If required, modifications will introduce a metatarsal bar to increase the surface contact area proximal to the ROI(s) and increase the metatarsal bar's size by extending its length to the distal point of the medial longitudinal arch.

3.2.3 Modelling process of the optimised insole algorithm

In line with step three of the MRC guidance which outlines the modelling process for the intervention, the optimised insole algorithm was developed. The algorithm standardised the design and modification of insoles, classified according to walking gait profiles derived from temporal profiles. A key part of the process for the development of the algorithm involved stakeholder engagement.

3.2.3.1 Stakeholder involvement in the optimised insole algorithm development

Key stakeholders were involved throughout the development and design of the optimised insole algorithm. For the design and development of the optimised insole algorithm, engagement with stakeholders occurred from the commencement of the PhD journey. Identifying and working with stakeholders can have constructive impacts upon every research process stage (Shippee *et al.*, 2015). Table 3.2 displays a list of the stakeholders involved from conception to evaluation and the nature of their contribution. Their involvement was iterative with frequent discussions and engagement at regular intervals.

Table 3.2 List of stakeholders involved in developing the optimised insole algorithm

Stakeholder group	Involvement	Contribution
Patients with diabetic foot ulceration or history of diabetic foot ulceration	Consultation and co-production	• Provided patient journey • Proof-of-concept feedback • Contributed to algorithm design and acceptability
Podiatrists (Musculoskeletal specialists)	Consultation	• Provided feedback on algorithm concept • Provided feedback on insole manufacture, techniques, modifications and optimisation • Provided expert group feedback on the algorithm
Podiatrists (wound specialists)	Consultation	• Provided feedback on algorithm concept
Orthotists	Co-production	• Provided feedback on Pulman-house shoe • Provided expert group feedback on the algorithm
Commissioners of NHS Diabetic foot services	Consultation	• Provided context of diabetes service delivery
Podiatry Head of services	Consultation	• Provided context of insole and footwear delivery in clinical services • Provided parameters (cost, time, resources) for clinical use of the algorithm
Casting technicians	Co-production	• Provided feedback on insole theory

3.2.3.1.1 Expert clinicians

Expert clinicians were consulted for their views on the optimised insole algorithm (Table 3.2). Expertise was utilised from clinical and research settings based on their knowledge and skills associated with footwear and insole provision and the use of an in-shoe measurement system. An additional criterion was stipulated requiring involvement with the assessment and treatment of patients with diabetic foot pathology.

The expert clinicians provided feedback on the proof-of-concept of the optimised insole algorithm at the beginning of the project. They identified a plethora of features that were used in clinical practice to design insoles. This discussion on insole manufacture, techniques, modifications and optimisation led to the systematic review's specific aims to inform the development of the algorithm.

The expert group additionally provided feedback on the draft version of the optimised insole algorithm. Clarification on the definitions of the features of the insoles and application of the Fscan system to identify gait patterns in a clinical environment were identified. These improvements informed the composition of the training manual for the delivery of the algorithm.

3.2.3.1.2 Heads of Podiatry Services, Clinical Commissioners of diabetic foot services

Three Heads of Podiatry NHS Services and the Devon Clinical Commissioner for diabetic foot services were consulted to develop the optimised insole algorithm. Their perspectives were explored to understand the operational context in which the algorithm would be used and provide a mandate. Concerns emerged on the in-shoe technology costs, increased length of appointment times, and assurance on the proposed cost offsetting associated with replacing existing footwear and customised insole provision. The concerns were addressed by highlighting the acquirement of excess treatment costs for this research project. The innovation of the optimised insole algorithm was welcomed in the impetus to reduce the risk of DFU and lower limb amputation.

3.2.3.1.3 Patients and participant involvement

Patients and participant involvement (PPI) occurred throughout the optimised insole concept and algorithm design stage. PPI involvement refers to the practice of patients, members of the public and researchers working together to prioritise, plan, conduct and disseminate research (Dudley *et al.*, 2015; NIHR, 2019b).

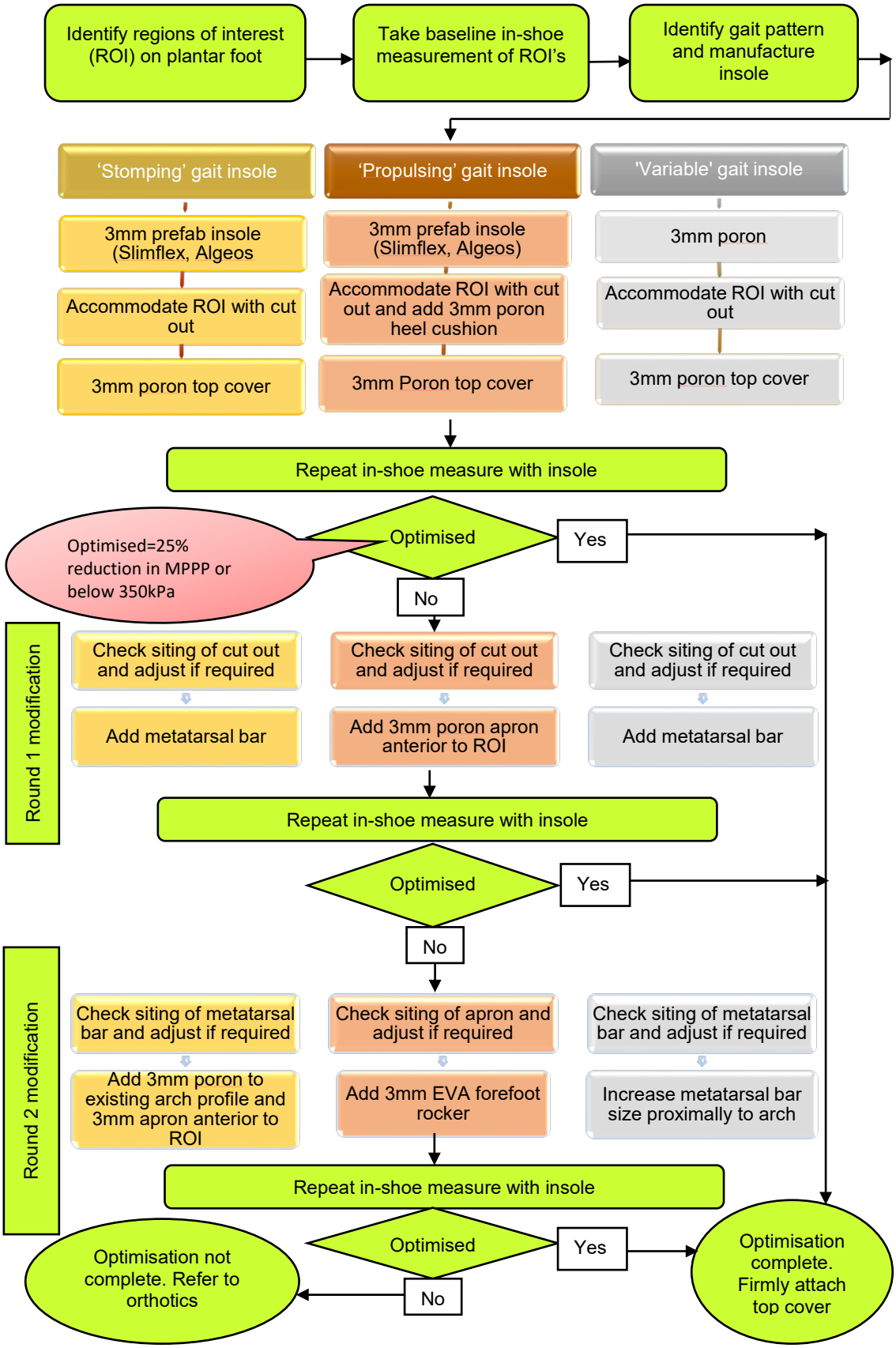
Patients were consulted on the insole design iterations throughout the algorithm's development, giving feedback on the look, comfort and ease of use. One of the patients, in particular, became very engaged in the process and agreed to serve on the trial management group as a PPI representative. In conjunction with the proof-of-concept pilot work, this information was used to inform key aspects of the feasibility trial protocol and outcome selection.

3.2.4 Optimised insole algorithm

The optimised insole algorithm (Figure 3.4) aims to reduce the risk of DFU in people with DPN by identifying areas of the foot at risk of developing a diabetic foot ulcer and providing insoles that reduce MPPP to below a perceived safe threshold at that same outpatient visit. This algorithm demonstrates novel thought in its application by guiding any clinician with basic competence in insole manufacture to design and issue insoles to patients with DPN. The insole and its constituent design and features are dependent on classifying the patient into one of three walking gait pattern types described in Chapter three, section 3.2.2.1, identified by analysing force-time curves from the in-shoe pressure analysis system. The ability to measure the insole's effectiveness with real-time dynamic walking data from the in-shoe system can demonstrate if MPPP has

been effectively reduced below the target thresholds for DFU occurrence. Opportunities to refine the insole by up to three rounds of instant modifications, guided by the walking gait pattern, provides confidence that the insole is more likely to reduce the magnitude of the MPPP to below the set thresholds.

Optimisation of peak plantar pressure reduction in the optimised insole algorithm was defined as first below a magnitude of 350 kPa, or if this magnitude was not reached then a decrease of 25% from baseline. Optimisation relates to a threshold magnitude for plantar pressure when wearing insoles and footwear where DFU risk is assumed to be reduced. The absolute value of 350kPa was derived from the work of Paton et al. (2014), where peak pressure with a prefabricated insole compared to baseline was 363kPa (Paton *et al.*, 2012). The selection of a peak pressure reduction of 25% from baseline was because of its association with a threshold of re-ulceration in people with a diabetic foot ulcer with a standardised insole (Ulbrecht *et al.*, 2014).



ROI-Regions of interest; mm-millimetres, MPPP – Mean peak plantar pressure, EVA- Ethylene-vinyl acetate, kPa-kilopascals

Figure 3.5 Optimised insole algorithm

3.3 Chapter summary

This chapter has described the development of the optimised insole intervention. Presenting a coherent, evidence-based approach when developing an intervention can reduce the risk of its loss or non-adoption in the real-world setting (O'Cathain *et al.*, 2019). The development of the optimised insole intervention commenced with the proof-of-concept. Using a step-by-step approach, as advocated by the MRC framework, the concept of optimising insoles was advanced. After identifying and evaluating the literature base, the theoretical construct of using temporal load patterns and plantar pressure analysis to inform the design and modification of insoles was discussed. Along with stakeholder engagement and the systematic review findings, the optimised insole algorithm was developed which underpins the optimised insole intervention.

Having developed the optimised insole algorithm, the next step was to assess the feasibility of its delivery and the proposed evaluation methods before undertaking a definitive trial to determine its clinical and cost-effectiveness. Following recommendations from the MRC framework the next chapter will present the feasibility study methods. The intention of the feasibility study was to allow the operational experience to inform the conduct and final design of an anticipated definitive trial so that the optimised insole algorithm can be successfully evaluated and delivered with confidence.

Chapter 4 Methods

This chapter presents the rationale and methodology of the Insoles to Ease Pressure (INSTEP) feasibility randomised controlled study. The methodology for the fRCT is described below and can also be found in the published protocol, Appendix 1 (Collings *et al.*, 2019). Having developed the optimised insole intervention, the next step of the MRC framework is the feasibility or pilot stage (Craig *et al.*, 2008). Undertaking a pilot or feasibility study addresses acceptability, compliance, delivery of the intervention, recruitment and retention of participants, and inadequate effect sizes before full-scale evaluation (Eldridge *et al.*, 2016b).

4.1 Research philosophy

Understanding the philosophical and theoretical approach to research is important to appreciate the decisions that influenced the research process (Moon & Blackman, 2014). Philosophical and theoretical position informs methodological and interpretative decisions of researchers (Hathcoat, Meixner & Nicholas, 2017). Philosophical approaches are based on the concepts of ontology and epistemology. Different ontological and epistemological positions can lead to contrasting approaches towards the same phenomenon (Scotland, 2012).

The practical and applied nature of this research prompted the adoption of a pragmatic philosophical approach. Pragmatism is founded on ontological and epistemological positions that can be positioned between the two extremes of subjective and objective human values (Ansari, Panhwar & Mahesar, 2016).

Pragmatists believe that there cannot be a single reality but multiple realities and that a mix of approaches that are most appropriate to fulfil the aims and objectives of the research question should be used to find the truth (Creswell & Clark, 2017; Johnson & Onwuegbuzie, 2004; Tashakkori & Teddlie, 2009).

Several influential factors were responsible for adopting a pragmatic approach for this study. As a manager and clinician working within the NHS, the research question and design is based on real-world experiences (Cresswell & Plano Clark, 2011). Accordingly, there is a gap in the literature and a desperate need to provide high-quality evidence for therapeutic footwear and insoles to reduce the risk of DFU and inform clinical practice. Furthermore, any intervention must be fit for adoption in the NHS and overcome multiple barriers to implementation. This requires a pragmatic approach that recognises the everyday challenges of implementing novel, evidenced-based solutions into practice. This approach aligns with the complexity of managing patients with DPN, which recommends a patient-centred approach (Gethin *et al.*, 2020). Recognising the multiple factors associated with reducing the risk of DFU and the existing constraints of the NHS meant that a single truth would not be appropriate, but rather multiple truths that are founded in a pragmatist approach.

4.2 Methodological approach

At the outset, there was considerable debate amongst the trial management group as to whether a feasibility or pilot design should be chosen. There are no definitive criteria to differentiate using a feasibility or pilot design as part of the MRC framework, although pilot and feasibility studies serve an important role

when determining the most appropriate definitive trial design (Blatch-Jones *et al.*, 2018).

This uncertainty of definition was perhaps representative of the wider debate in the literature over feasibility or pilot terminology. Eldridge et al. (2016) suggests the lack of clarity and agreement for each approach reinforces the interchangeability of each design (Eldridge *et al.*, 2016b). Some authors highlight the cross-overs of both designs, suggesting all pilot studies are feasibility studies but not all feasibility studies are pilot studies (Donald, 2018; Whitehead, Sully & Campbell, 2014). Other authors suggest more distinctive criteria for each design approach. Arain et al. (2010), for example report that pilot trials use the same design and method as the subsequent larger main trial (Arain *et al.*, 2010). In contrast feasibility studies are designed to build the foundation for the planned intervention study (Orsmond & Cohn, 2015).

Using the definitions from Thabane et al. (2010), a feasibility study design was chosen to address relevant research questions on the estimation of recruitment, retention and adherence rates for the anticipated larger study (Thabane *et al.*, 2010). Additional uncertainties over the delivery of the therapeutic footwear and insole, the effectiveness of the blinding and the selection of the most appropriate outcome measure provided further endorsement of a feasibility design. These uncertainties are frequently cited in many aspects of diabetic foot trial design and reporting (Game *et al.*, 2016; Jeffcoate *et al.*, 2016).

The importance of adopting a feasibility design became more apparent throughout the course of the study. The uncertainty with delivering the study procedures and the insole intervention, that at the outset appeared unfounded

to the author, became more prominent during the study. In particular, recruitment and retention of participants was more problematic than expected. Additionally, the delivery of the insole intervention in its existing format would not have satisfied the criteria of representing a smaller scale version of the main RCT, precluding that of a pilot study design. Consequently, the feasibility design will inform the development of the large scale anticipated RCT, which will increase the chances of a successful full-scale study and is considered to be a more efficient use of research resources (Morgan *et al.*, 2018).

When undertaking feasibility or pilot work, guidance from the MRC framework recommends a mixture of qualitative and quantitative methods (Craig *et al.*, 2018b). When used together, a quantitative and qualitative methods approach can provide a balanced approach and allow for more complete analysis (O'Cathain, Murphy & Nicholl, 2010; Tashakkori & Teddlie, 2009).

This study used an approach with a qualitative method embedded in a quantitative RCT design (Plano Clark *et al.*, 2013). This approach integrates both quantitative and qualitative data and findings interdependently to address a common goal (Richards *et al.*, 2019), and is becoming increasingly popular in the context of health and health service research (O'Cathain *et al.*, 2015). Although the use of quantitative and qualitative methods together has been termed by some authors as a 'mixed methods' approach (Tashakkori & Creswell, 2007), Timans et al. (2019) argue that the term mixed methods is a contradiction, derived from researchers using multiple or combined methods (Timans, Wouters & Heilbron, 2019). The authors suggest in true epistemological terms, it is the mixing of paradigms rather than methods.

Consequently, the approach of embedding a qualitative method in the RCT can be viewed as laying between the quantitative paradigm, based on objectivism and positivism, and the qualitative paradigm, based on subjectivism and interpretivism (Cresswell & Plano Clark, 2011; Tashakkori & Creswell, 2007).

The value of using this approach became apparent when undertaking the participant interviews. Listening to the participant's experiences was particularly thought-provoking to the author, where the prominence of patient-centred care became increasingly noteworthy. In particular, the individuality of participant's experiences of living with diabetes was enlightening and hugely informative when considering the anticipated RCT design and also the complexity of reducing the risk of DFU. Consequently, the contribution of the embedded qualitative aspect to the study design and future care-pathway innovation was extremely valued.

4.3 Quantitative phase – feasibility randomised controlled trial

An RCT design was decided for the quantitative aspect of the feasibility study. RCT's are considered the gold standard for evaluating the efficacy of clinical interventions and seek to ensure high standards of internal and external validity (Spieth *et al.*, 2016) while removing as many sources of bias as possible (Ahuja, 2019). Adopting this design for the fRCT considered the feasibility and acceptability of the randomisation process for the future anticipated RCT. Randomisation is essential to mitigate bias by randomly allocating subjects to treatment and control groups under no pretence of rule or predictability (Lim & In, 2019). This implies that subjects get an equal chance of receiving each treatment, which generates comparable intervention groups, similar in all

respects except for the intervention each group receives (Suresh, 2011). This similarity allows for statistical inferences on the differences between treatment groups (Altman & Bland, 1999).

The design and composition of the intervention comparison group for this fRCT was considered at length to satisfy the essential requirements to provide discriminatory evidence of a treatment outcome for the definitive RCT. The composition of the comparison group is often a compromise of different influencing factors. Protecting participants' interests, using study resources effectively with maximum findings validity and providing a treatment effect to answer the study question are some factors previously cited (Gold *et al.*, 2017). Moser (2020) discusses the different concepts of control treatments, each with their own methodological and ethical implications (Moser, 2020).

For this fRCT, an active control was provided as the comparator group. The provision of an active control insole served as a credible alternative to the optimised insole, whilst allowing a treatment effect size to be calculated. Therefore, the acceptability of the active insole as a comparator would be evaluated. Other studies investigating the effect of footwear and insoles in reducing the risk of DFU have used active controls (Barnett, 2002; Bus, Ulbrecht & Cavanagh, 2004; Martinez-Santos, Preece & Nester, 2019; Parker *et al.*, 2019).

One important feature of the active control group evaluation is its contribution to the blinding process. Blinding process is regarded as an important feature to control internal validity in RCT’s (Spieth *et al.*, 2016). Blinding of participants, intervention providers and outcome assessors is intended to eliminate bias

associated with human behaviour (Day & Altman, 2000). Two systematic reviews have described biased effect estimates in RCT's, after reporting exaggeration of odds ratios by non-blinded assessors (Hróbjartsson *et al.*, 2012) and participants (Hróbjartsson *et al.*, 2014). However, a more recent meta-epidemiological study contradicted these findings, by reporting no difference in average estimated treatment effect between trials with and without blinding for participants, intervention providers, or outcome assessors (Moustgaard *et al.*, 2020). Despite this finding, the authors concluded more confirmatory evidence is required before omitting blinding in study designs.

The effectiveness of the blinding of participants and outcome assessment to the insole intervention was also evaluated. The blinding process in studies involving insole interventions is notoriously difficult due to the difficulty in concealing the intervention from participants, providers and assessors (Bonanno *et al.*, 2015). Concealment of the insole intervention to the providers was considered, but their role in manufacturing and providing the intervention made blinding impractical. Lack of provider blinding can reduce the internal validity of a trial, putting more importance on the rigour of the randomisation process to reduce performance bias (Boutron *et al.*, 2007).

Yet limitations of RCT's exist which challenge their hierarchical place in evidenced-based medicine. In the current COVID-19 era, the surpassing of RCT evidence to implement urgent and needed interventions have been highlighted as a 'scientific and moral imperative' (Greenhalgh, 2020). The RCT's inflexible approach to establish evidential interactions, as opposed to explore, confines the results and the context to which they are applied. Authors

suggest that the linear logic of the traditional RCT approach is outdated by the complexity of designing and delivering interventions in modern health care (Greenhalgh & Papoutsi, 2018). By way of their design, RCT's will only answer a proportion of the questions posed by a system (Cohn *et al.*, 2013). A fRCT will only be able to provide effect-size estimates rather than fully powered statistical effects. It will not answer the important research questions of participant and clinician acceptability.

4.4 Embedded qualitative study

Using a concurrent data collection approach, purposive sampling was used to select a sample of participants and podiatrists to undertake semi-structured interviews for the embedded qualitative component of the fRCT. A thematic analysis approach was then applied for the analysis. This approach was selected to address uncertainties around the acceptability to study participants, and delivery to podiatrists, of the optimised insole. Giving voice by exploring study participant and clinician experience can provide valuable insight into the procedural, methodological and clinical issues of the study (Braun & Clarke, 2006). These experiences are crucial to refine the design of a research study (Nickinson *et al.*, 2020).

The opportunity to adopt an open, inquisitive approach is the foundation of qualitative approaches, where the emphasis is on broad discovery, rather than specific focus. Critics contend that qualitative approaches lack generalisability, validity and reliability (Rolfe, 2006; Sandelowski, 1993). An alternative perspective asserts that qualitative approaches also design, collect, analyse and interpret data in the same way as quantitative approaches (Choy, 2014),

thereby holding the same empirical status. Thematic analysis employs such structure, by identifying, analysing, organising, describing and reporting themes within a data set (Braun & Clarke, 2006). It also provides a flexible, structured approach to analysis (Clarke & Braun, 2017). Critics of the thematic analysis approach highlight the lack of substantial literature to substantiate its position amongst other established, qualitative approaches (Nowell *et al.*, 2017). Other disadvantages of the thematic analysis approach are the inability to make claims about language use (Braun & Clarke, 2006) and the inconsistency from an overly flexible approach (Vaismoradi, Turunen & Bondas, 2013). Braun and Clarke (2020) advocate the significance of using a structured, vigorous approach when undertaking thematic analysis to avoid such quality issues (Braun & Clarke, 2020).

In this fRCT, both quantitative and qualitative data were collected at the same time with integration of the overall data and findings for analysis and interpretation (Creswell, 2014). However, by virtue of its embedded role, the qualitative findings had less weighting than the quantitative RCT aspect. Nevertheless, the combination of both the RCT and embedded qualitative study enabled a deeper understanding of the fRCT data and findings and the implications for the anticipated future RCT. Having established the foundations and rationale for the methodological approach, the next section will describe the methods of INSTEP study.

4.5 Study design

This was a participant and assessor blinded, randomised multi-centre parallel group feasibility trial with embedded qualitative study. Participants were

randomised to receive either an optimised insole and Pulman-house shoe plus usual care (intervention), or flat, poron insole and Pulman-house shoe plus usual care (active- control). A sub-group of study participants with diabetes, and podiatrists delivering the intervention, were interviewed to explore their experiences of receiving/delivering the intervention.

The protocol (Collings *et al.*, 2019) was informed by the SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials (Chan *et al.*, 2013). The Consolidated Standards of Reporting Trials (CONSORT) (Boutron *et al.*, 2017; Moher, Schulz & Altman, 2001) and Template for Intervention Description and Replication (TIDieR) (Hoffmann *et al.*, 2014).

4.6 Study aim

The aim of this feasibility study was to obtain the necessary information and estimate important parameters needed to inform the protocol development of an anticipated multi-centre RCT (Eldridge *et al.*, 2016b). This future study would compare the clinical and cost effectiveness of an optimised insole plus usual care with an active control insole plus usual care for people with DPN.

4.6.1 Objectives

The objectives of this feasibility study were to:

- Assess the feasibility and acceptability of the trial procedures comparing the effectiveness of an optimised insole and Pulman-house shoe plus usual care with an active control insole and Pulman-house shoe plus usual care for people with DPN;

- Assess the appropriateness and performance of outcome measures to select the most appropriate primary and secondary outcome measures and inform the sample size calculation of the future RCT;
- Explore the experiences of participants' receiving optimised insole and Pulman-house shoe with an active control insole and Pulman-house shoe, and podiatrist's experiences of delivering the intervention.

4.7 Ethical and regulatory considerations

The protocol, V.1.0 (12/7/2017), was reviewed by the South-West Exeter Research Ethics Committee (REC) and given a favourable opinion (REC ref: 17/SW/0169) on 18 September 2017 (appendix 2). Health Research Authority regulatory approval was given on 19 September 2017 (appendix 3) and the study was adopted on the NIHR portfolio on 15 October 2017 as IRAS project ID: 224903; Protocol number: FHHS-224903-RC-022; Trial register number: ISRCTN16011830. The University of Plymouth was the sponsor of the study.

There were two amendements to the study protocol:

1. 12/12/17 Change of PI due to maternity leave from Dr L Cherry to Dr Cathy Price for Solent site
2. 31/05/18 Introduction of poster for patient recruitment, as proposed by the PPI representative at the trial steering group

4.8 Study setting

The feasibility study was conducted between November 2017 and January 2019 at three study sites located in the south-west of England (Figure 4.1). Historically, diabetes-related major and total lower limb amputation incidence

has been very high across most of the South-West region. For example, between 2005 and 2007, Torbay experienced major amputation rates of 3/1000/year compared to a national average of 1.1/1000/year (Paisey *et al.*, 2018). This variation is associated with differences in demographics, where an aging population and higher proportions of people with diabetes and its co-existing complications are present compared to other areas of England. In 2019, south-west England was estimated to have a higher proportion of adults aged over 65 (23%), compared to the national average of 18.5%. This ranged from 26.9% in Torbay to 20.4% in Solent.

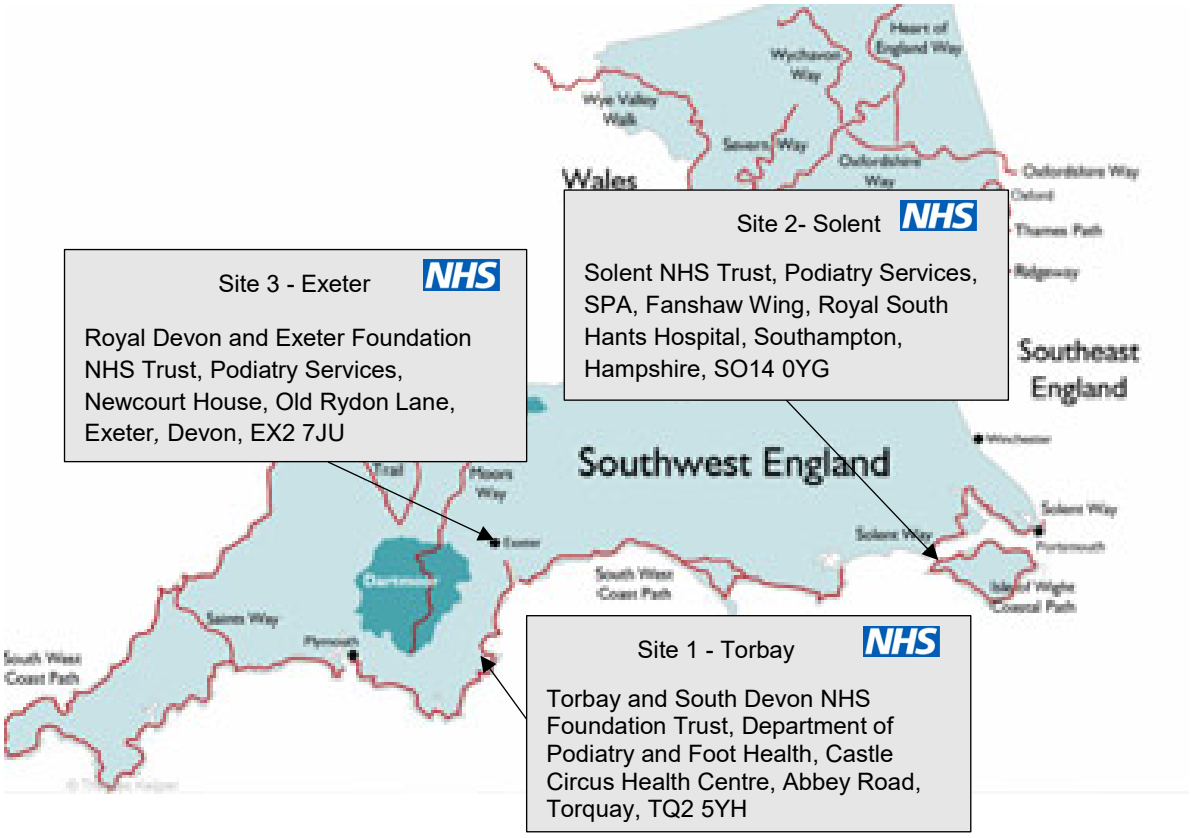


Figure 4.1 Locations of study sites

4.9 Sample size

As a feasibility study, no formal power calculation was undertaken (Eldridge *et al.*, 2016b). However, based on initial findings from pilot work (Instant insole enhancement for the prevention of foot ulcer recurrence in people with diabetes using an in-shoe pressure measurement technology: A randomised control trial pilot study: REC reference: 13/SW/0310, 13 June 2014, IRAS project ID: 138428 Unpublished), a sample size of 76 was calculated. This was based on an estimate of an adherence rate of 70% to within a 95% confidence interval of +/-10%. The aim was to recruit 26 patients per site over 16 months, with an overall recruitment target of two per month per site.

4.10 Recruitment

Potential participants were identified by the podiatry clinical team at each of the participating sites during a routine appointment within either the multidisciplinary diabetic foot clinic or podiatry community clinic. Podiatrist's identified potential participants and only those appearing to meet the eligibility criteria for inclusion in the study were approached. Potential participants were given a brief verbal explanation of the study by the podiatrist and provided with a Participant Information Sheet (PIS). The study was adopted onto the UK Clinical Research Network (CRN) portfolio.

4.11 Eligibility criteria

Eligibility criteria were informed by the literature from relevant research studies, discussions with podiatrists who treat people with diabetes and patient representatives. Eligibility criteria can affect recruitment and retention and

influence the external validity of the study findings (Kennedy-Martin *et al.*, 2015). In keeping with a pragmatic study design, the inclusion and exclusion criteria were kept broad. It was important to ensure those recruited were representative of the patient population, and would be generalisable and relevant to those with DPN and DFU (Rothwell, 2005).

4.11.1 Inclusion criteria

Inclusion criteria were selected for their relevance to the causal pathway to DFU. In particular:

- Confirmed diagnosis of type 1 or 2 diabetes as recorded in participant's medical notes;
- Aged over 18 years;
- Identified clinical need for insoles by podiatrist (requiring referral for plantar foot offloading devices due to recently healed or healing ulcer site on the weight-bearing plantar surface of the foot and/or pre-ulcerative callus formation). Those people wearing existing insoles that either needed replacing because of excessive wear or were no longer meeting the clinical need were considered for inclusion. However, confirmation was required that the patient had stopped wearing the insole for at least one month since a 'wash-out' period was required before inclusion;
- Neuropathic (sensory DPN, defined as insensitivity of a 5.07/10g monofilament at one of three sites: the plantar aspects of the great toe, third, and fifth metatarsal heads (Feng, Schlösser & Sumpio, 2009; Mueller, 1996);
- Palpable pedal foot pulses;

- Able and willing to comply with all trial requirements.

4.11.2 Exclusion criteria

Exclusion criteria were selected to safeguard participants during the study procedures and by rejecting potential participants with other existing risk factors for DFU. In particular:

- Any other significant disease or disorder which, in the opinion of the principal investigator (PI), may put the participant at risk of health deterioration, such as falls, because of their involvement in the trial;
- Non-healing foot ulcer at another site on the plantar aspect of the foot that requires targeted off-loading;
- Unable to walk five metres with or without walking aid;
- Unable to stand on either leg independently for 10 seconds (with or without a chair to assist balance);
- Lacking capacity or unwilling to give consent;
- Already wearing existing insoles that are clinically appropriate as determined by the treating clinician;
- Peripheral vascular disease (non-re-constructible vascular disease recorded in their medical notes as determined by arterial duplex and clinically assessed by a vascular consultant);
- Unwilling to wear therapeutic footwear;
- Gross foot deformity e.g. charcot foot or fixed rear foot deformity;
- Where major amputation of the foot has occurred (ray or trans-metatarsal amputation of the ulcerated foot).

4.12 Screening

Following identification of potential participants, screening was undertaken by a CRN staff member who contacted the individual after a minimum of 24 hours of them receiving the PIS, to discuss the study in more detail and provide the opportunity for them to ask further questions. The CRN staff member confirmed eligibility through a series of screening questions. If eligibility criteria were met, a podiatry appointment was arranged, where final confirmation of eligibility was undertaken.

4.13 Consent

In line with Good Clinical Practice (GCP) the PI at each site had overall responsibility for the informed consent of participants at their site. Any participant who was willing and eligible to participate in the study was asked to complete and sign an Informed Consent Form (ICF) at the initial baseline visit. This was countersigned by the CRN staff member or podiatrist taking consent. Consent was also sought to contact the participant's general practitioner to inform them of their participation in the study. A copy of the completed consent form was provided and a further copy filed, together with a copy of the PIS, in the participant's podiatry records.

4.14 Randomisation

Following baseline assessment by the podiatrist, eligible participants were randomised to one of two groups: one group received the optimised insole designed to reduce peak plantar pressure in addition to usual care (optimised insole group); while the other group received the active control insole in addition

to usual care (active control insole group). The Peninsula Clinical Trials Unit (PenCTU) generated the randomised allocations by computer, in conjunction with an independent statistician, and in accordance with a standard operating procedure. Participant's details were entered into the randomisation website by the podiatrist after the baseline assessment. The podiatrist immediately received an email indicating the group allocation of the participant.

A minimisation procedure was used to reduce the risk of bias by ensuring equal numbers of participants in the two allocated groups by study site and by previous DFU status. Bias may occur within random sampling when there are differences in the clinical and demographic characteristics of the participants receiving different treatments (Altman & Bland, 1999). In this study, the inclusion of participants with and without previous DFU introduced potential bias. This was because plantar foot pressures and risk of DFU are higher in subjects with a history of a diabetic foot ulcers than those without, introducing variability in outcome determinants within this study population. Similarly, the use of minimisation to reduce potential imbalance across sites in a multi-centre study is advocated (Brown *et al.*, 2005).

The advantage of using a minimisation procedure to lessen the risk of bias ensures group allocation is designed to reduce any difference in the distribution of known or suspected determinants of outcome (Treasure & MacRae, 1998). This prevents the overestimation or underestimation of the difference of treatment effect between the active control and optimised insole. However, minimisation is considered a non-random method of treatment allocation by some authors (Scott *et al.*, 2002). Other methods of randomisation such as

simple, permuted block and stratification randomisation equally have strengths and weaknesses when considering use in a RCT. Allocation by simple randomisation will often achieve well-balanced groups, especially in larger trials (Scott *et al.*, 2002). However, simple randomisation does not take into account baseline covariates, which can cause imbalances in group allocation, especially in smaller trials such as this (McPherson, Campbell & Elbourne, 2012). Controlling for the influence of pre-specified covariates ensures balance between group allocations (Lachin, Matts & Wei, 1988). Block randomisation ensures allocation proportions are exactly achieved by assigning participants into groups over time (Broglio, 2018). Although treatment assignments within blocks are random, there is the potential for bias if treatment assignments become known or

predictable and this technique does not control for covariates, which was required for this study (Matts & Lachin, 1988). Stratification randomisation generates a strata for each combination of pre-specified covariates, and participants are assigned to the appropriate strata of covariates (Kang, Ragan & Park, 2008). This method requires all participants to be identified before randomisation occurs, which is not appropriate in a study where participants are recruited continuously, which was the recruitment strategy for this study. Resultantly, a minimisation strategy was appropriate for this study.

4.15 Blinding

The majority of outcome measures were undertaken unblinded, by the podiatrist, during the delivery of the study procedures. The podiatrists were unable to be blinded to the intervention as they manufactured and provided the

optimised and active control insole. The Chief Investigator (CI), who was not involved in the delivery of the insoles, blind assessed diabetic foot ulcer status by reviewing anonymised photographs of ulceration/callus status of the feet independently. Batches of anonymised photographs were made available to the CI through the web-based data collection by the PenCTU on a monthly basis to minimise unblinding. A blinding form was completed at the conclusion of each batch by the CI.

Every effort was made throughout the study to ensure participants were blinded to their group allocation. The optimised insole and active control insole received identical top covers to minimise discovery of group allocation. Insoles were fitted into the participant's house shoe by the podiatrist to minimise handling and inspection of the insole by the participant. Peak pressure data was not revealed to the participant to minimise the potential for unblinding. A blinding form was completed by the study participant at each measurement session.

4.16 Study insoles

4.16.1 Pulman-house shoe

For both groups, the allocated insole was housed within a Pulman-house shoe. The Pulman-house shoe is considered a therapeutic shoe that combines key features of width and depth, suitable to reduce complications from footwear for people with DPN (Figure 4.1). The front and rear of the shoe open up using Velcro® fastening to allow easy access and adjustability for the wearer. The materials are waterproof to enable use outdoors.

Figure 4.1 Pulman-house shoe

The Pulman-house shoe was used in this study for three reasons. Firstly, it could be issued to participants to use as a substitute therapeutic shoe whilst waiting for the therapeutic footwear from the orthotist. Feedback from participants involved in the early pilot work indicated that the Pulman-house shoe was acceptable. Secondly, using a Pulman-house shoe standardised the footwear for measuring in-shoe plantar pressure measures with the active control and optimised insole. Standardising footwear across groups reduces confounding on the treatment effect of the insole. One small scale study reported consistent directional differences across standardised footwear control conditions for healthy participants (Lewinson & Stefanyshyn, 2015). However, the authors argued that wider than expected biomechanical effects were found amongst participants in different footwear conditions, suggesting that participants should use their own footwear in future clinical studies. Lastly, because footwear and insoles are only effective in reducing peak plantar pressures if worn, providing the Pulman-house shoe was expected to increase the wear time of the insoles and footwear. By enabling participants to wear the trial insole in the Pulman-house shoe when at home, in addition to transferring the insoles into other footwear as part of usual practice, the compliance of

participants to using the insoles and footwear was expected to increase. Compliance and adherence to prescribed footwear and insoles is traditionally low in people with DM (Knowles & Boulton, 1996). One study reported that 58% of DPN wear their prescribed footwear for less than the 60% of daylight hours (Arts *et al.*, 2014). Part of the problem is that those with DPN take off their prescribed therapeutic footwear whilst at home. In a cohort study of people at high risk of ulceration, adherence to wearing therapeutic footwear and insole at home was 61% (± 32%) compared to 87% (± 26%) when away from home (Waaijman *et al.*, 2013). They also reported that walking activity was higher when at home (3,959 ± 2,594 steps) compared to when away from home (2,604 ± 2,507 steps), putting an “at risk of ulceration” foot at an even greater risk.

4.16.2 Optimised insole group (intervention)

The optimised insole group received instant customised insoles (Figure 4.2) designed and optimised using the Fscan in-shoe pressure analysis system (Tekscan, Boston, MA) and a Pulman-house shoe. Baseline mean peak plantar pressures (MPPP) were assessed by the podiatrist and the data used to inform the design of the optimised insole for those allocated to this group.

Figure 4.2 Optimised insoles from medial view and dorsal view

The optimised insole design and modification(s) was informed by the optimised insole algorithm, described in Chapter three, section 3.2.4. In summary, this insole optimisation was prescribed according to one of three walking gait patterns for people with DPN, described in Chapter three, section 3.2.2.1. The optimised insole consisted of a pre-constructed base to conform to concavo-convex contours of the foot (Slimflex Full length Medium Density (Shore A50), Algeos, UK). Regions of interest were identified to accommodate for prominent areas, previously ulcerated areas or areas of high mean peak plantar pressure. These areas were targeted with modifications designed to offload pressures. These modifications were used to reduce mean peak plantar pressure values in conjunction with real time pressure data from the Fscan system in the specific regions of interest.

4.16.3 Active control insole group

The active control insole group received a three-millimetre (mm) flatbed insole of Poron 4000 with a four-mm medium density heel lift (Figure 4.3) and a Pulman-house shoe. Previous research demonstrated that a three-mm flat medium density polyurethane (Shore A hardness 55 ± 3) insole reduced peak pressure under 1st MTPJ by 35kPa compared to shoe only condition in healthy participants (Healy, Dunning & Chockalingam, 2011). Flat insoles are also considered biomechanically inert (Chapman *et al.*, 2015), although some authors contradict this belief (Lewinson & Stefanyshyn, 2015).

Figure 4.3 Active control insole from medial view and dorsal view

The use of an insole as an active control that reduced plantar foot pressure was deliberated on at length when designing this study. Although a placebo control is considered the most rigorous comparator when designing a clinical trial, the use of an active control is frequently required (Sutherland, 2007). Employing an active control can satisfy ethical standards by not exposing participants to unnecessary research risk (Horng & Miller, 2003), whilst still providing a comparator to the intervention.

The rationale for using an active control in this study was threefold. Firstly, when undertaking proof-of-concept pilot work, clinician's felt that participants were endangered by not providing a plantar foot pressure reducing insole to those at risk of DFU. Therefore, the active control insole was expected to reduce plantar foot pressures, albeit with an unknown effect size compared to the optimised insole, and unknown impact on reducing the risk of DFU. This satisfies the criteria for equipoise and clause nine of the Declaration of Helsinki, whereby new treatments should be tested against those of current methods

(Tollman *et al.*, 2001). Secondly, the active control insole was used as it was identical to the top-cover of the optimised insole, thereby providing a credible alternative and contributing to the blinding process (Herbert *et al.*, 2011). Finally, the active control standardised the treatment given to participants across the different sites, whereby usual treatment pathways differed.

There are implications when using an active control approach. The use of an active control influences treatment effect, requiring different inferential statistics (Temple & Ellenberg, 2000). If the size of the treatment effect and confidence intervals are too small, then distinguishing between the active control and intervention may be difficult, and a non-inferiority approach to study design required. For this study, it was expected that the treatment effect size between the active control insole and optimised insole would be large enough to infer a clinically meaningful difference.

Participants from both allocation groups were provided with standardised information on footwear and insole usage, how to increase wear time of the insoles, foot self-inspection and what to do in the event of a ‘foot attack’ (an injury to the foot, such as diabetic foot ulceration, or signs of infection and/or sepsis). This information was reiterated at each appointment by the podiatrist. Participants were advised to contact the podiatrist should any problems occur, in order that they could advise on the management of these issues.

Trial insoles were replaced if excessive wear/damage was noted at any of the follow-up appointments and this was recorded in the case report form (CRF). Participants who forgot to bring their insoles to the follow-up appointments were offered another appointment in the following week to complete the Fscan

plantar pressure measures. Failure to complete any of the follow-up measures were recorded as missing data with reasons provided, where possible.

4.16.4 Usual care

During the 12-month period both groups accessed usual care services such as podiatry clinics for the management of foot care, wounds and ulcers. In line with current clinical practice this included a monthly podiatry assessment, as all participants were at high risk of foot ulceration (NICE NG19, 2015). Individual care plans comprised of a foot check, foot education, callus debridement and toe nail care, at not greater than three month intervals. In addition, participants were routinely referred to an orthotist for the provision of custom-made foot footwear and insoles.

Participants in both groups were asked to wear their trial insoles and house shoes when ambulating for a 12-month period or until they were provided with additional insoles/footwear by an orthotist. Once provided with insoles/footwear by the orthotist, participants were given the choice to alternate between wearing the ‘study’ intervention whilst at home and the orthotist’s devices when outdoors. Although this was not monitored, the amount of time the trial insole was worn was captured with the data logger.

For ethical reasons, any participant who developed a diabetic foot ulcer was immediately withdrawn from the study to receive appropriate treatment and an adverse event recorded. Those participants in whom the intervention was withdrawn to enable the required treatment, and who subsequently healed, were invited to continue with follow-up visits and assessments as planned.

4.17 Intervention fidelity

Intervention fidelity is the degree to which an intervention is implemented as intended in the original programme model or protocol by its developers (Slaughter, Hill & Snelgrove-Clarke, 2015). The MRC's earlier versions of the framework for developing and evaluating complex interventions lacked clarity when outlining intervention fidelity, which subsequent iterations have remedied (Craig *et al.*, 2018b; Craig *et al.*, 2020). Resolving challenges with delivering a complex intervention after its development can often help in its future clinical adoption (O'Cathain *et al.*, 2019). Developing a training package for delivering the optimised insole intervention and providing support to the podiatrist is a feature of intervention fidelity, promoting internal validity of the study.

4.17.1 Training package for delivering the optimised insole algorithm

The intention of the training package was to ensure consistency and uniformity in the delivery of the optimised insole algorithm. The training package, devised and delivered by the CI, comprised face-to-face training, provision of a treatment manual and familiarisation with the standard operating procedures needed to deliver the optimised insole algorithm. The variety of training elements aimed to mitigate for differences in the skill levels, experience, and implementation styles of the clinicians when delivering the optimised insole algorithm (Bellg *et al.*, 2004). The training package was delivered by the CI to three podiatrists who worked for different NHS Trusts. The podiatrists had been nominated by their service leads due to their pre-existing skills, and knowledge in providing insoles for offloading people with diabetic foot ulcers. All podiatrists

were musculoskeletal specialists, with a range of clinical experience ranging from five to 22 years post-graduation.

Face-to-face training consisted of a presentation on insole features and reducing the risk of DFU in people with DPN and a practical workshop on manufacturing insoles using the Fscan in-shoe system. This encompassed recognising gait patterns and optimising insoles in conjunction with the algorithm. Treatment manuals contained written details of the processes for manufacturing and delivering the insole and the standard operating procedures. Treatment manuals are considered a crucial step in complex intervention delivery (Blanche *et al.*, 2011). These were issued to the podiatrists at the face-to-face training day.

To ensure proficiency and consistency in the delivery of the optimised insole algorithm, a competency assessment was completed at the conclusion of the training session. This consisted of clinicians self-evaluating the extent to which they felt prepared to deliver the algorithm, and a practical assessment overseen and checked by the CI to provide an insole using the algorithm. This involved manufacturing an insole to offload a region of interest on a simulated patient. The three podiatrists felt ‘well’ prepared after the standardised training session to deliver the optimised insole algorithm.

4.17.2 Support to podiatrists

Following the training programme, ongoing support was provided to all podiatrists delivering the insole intervention. Ongoing support can prevent deviations from the intended intervention (An *et al.*, 2020). Support was

provided by the CI and consisted of a monthly newsletter, supplemented by three-monthly Skype calls and annual face-to-face visits to each site. The newsletter communicated prompts of key protocol requirements as well as describing study progress. The calls and visits allowed the podiatrist and CI to raise any specific issues that had arisen from delivering the insole.

4.18 Study procedures

Participants were asked to put on standard socks (20 denier stockings) and were fitted with a standard house shoe (Pulman, M. J. Markell Shoe Co. P. O. Box 246 Main Station, Yonkers, NY 10702-0246, U.S.A.). The Fscan system sensors were connected to a computer via a cuff unit and a 9.14 m long cable (Figure 4.4). Data was collected at a sampling rate of 50 Hertz (Hz) for four seconds. Sampling frequency refers to the number of samples measured by each sensor per second and recommendations suggest that pressure data collected between 45 and 100 Hz is adequate for walking (Chevalier, Hodgins & Chockalingam, 2010). Walking trials were undertaken in a clinical environment with a linoleum floor. A horizontal floor ensures the sensor surface is parallel to the ground to ensure the orientation of forces are perpendicular to the surface (Giacomozzi & Vaclav, 2011).

Figure 4.4 Participant using the Fscan system, insole and Pulman-house shoe

New sensors were provided for each participant for each individual foot, labelled and used to collect data from that foot throughout the duration of the study (Luo, Berglund & An, 1998). Appropriate acclimatisation to enable the sensors to reach a stable temperature was required for each participant. Wearing for five to 10 minutes prior to the calibration and recording of data reduces intra-sensor variation by 15% (Koch, 1993).

Before each data collection session each participant was weighed and each pair of sensors calibrated against body weight. Calibration refers to the process whereby the magnitude of the output signal of the sensor is related to the magnitude of the pressure acting on the sensor, although the error with this process can be as high as 14% (Woodburn & Helliwell, 1997). Static calibration was achieved by step loading, which is the application of known loads and recording the sensor output (Urry, 1999). Following calibration, if the sensor saturation pressure exceeded 2000 kPa the sensor was discarded. Calibration was checked for within-foot and between foot repeatability, and if excessive variation of ±10% was observed, the sensor was recalibrated.

Using a standardised protocol, participants were asked to undertake two test walks between chairs at their usual walking speed (Mueller *et al.*, 2003; Mueller *et al.*, 1994). Between the chairs a pre-marked five-meter (m) walkway with a minimum of 0.5m at each end to allow for deceleration and acceleration of gait was used to determine gait velocity (metre/second). This was calculated by stopwatch recording of the time taken to pass between the marks, and dividing distance (5m) by time taken (seconds) to walk between the marked lines to determine the preferred gait speed. The podiatrists monitored participants

walking speed to encourage consistency within walking trials (±5% deviation) to minimise the effect of cadence on pressure measurement (Burnfield *et al.*, 2004; Segal *et al.*, 2004). The test walks also allowed for the sensors to bed in and the temperature to reach equilibrium (Mueller & Strube, 1996a).

The walking tests were conducted immediately after the calibration. The test consisted of two walks initially; however, extra walks were used if gait velocity was not consistent (a maximum 5% deviation was allowed). The first and last steps were automatically discarded by the software to eliminate acceleration and deceleration effects, which are associated with slower walking velocities (Wearing *et al.*, 1999). This enabled a minimum of three mid-footsteps for peak pressure data collection to be analysed from each foot. Three mid-foot steps have been recommended for peak plantar measurement based on having excellent reliability (ICC≥0.90), although 12 steps are required for good validity (11 steps required for coefficient of variation ≤10%) (Arts & Bus, 2011).

Using the recorded Fscan data, a maximum of three ROI's across each feet were identified for each participant, where ROI=mean peak plantar pressure >350 kPa and/or was a recently healed ulcer site(s) or callus/corn formation. In addition, identification of type of gait pattern ('propulsing gait', 'stomping gait' and 'variable gait') by analysis of the recorded Fscan pressure time curve and force time curve occurred.

Immediately following randomisation, each participant received an optimised insole or active control insole. A specific process was followed for their design, receipt and measurement. Each participant repeated the two walking trials and the MPPP recorded for each ROI.

4.18.1 Plantar pressure measurement

Mean peak plantar pressure can be derived from in-shoe pressure measurement or platform based assessment (Chevalier, Hodgins & Chockalingam, 2010). The advantage of an in-shoe system is its portability, number of steps that can be analysed and practicality for walking gait detection events (Orlin & McPoil, 2000). However, when using an in-shoe measurement system, the sensors inside the shoe only measure vertical force. This is the force that is perpendicular to the surface and used in the calculation of pressure (Giacomozzi & Vaclav, 2011; Orlin & McPoil, 2000). It does not calculate shear or friction forces, which are implicated in the aetiology of DFU (Yavuz *et al.*, 2007).

Various in-shoe measurement systems are available, which differ in technology, size, sensor number and resolution. The Fscan in-shoe measurement system (Tekscan, Boston, Massachusetts, USA) is one system that is capable of reliable and repeatable data collection (Ahroni, Boyko & Forsberg, 1998; Catalfamo *et al.*, 2008; Mueller & Strube, 1996b). It can identify pressures from 960 sensing locations on the plantar foot, with a sensor size of 6.25mm², which is sensitive to detect localized peak pressures within a defined ROI (Giacomozzi & Vaclav, 2011). Recommendations from IWGDF suggest a maximum sensor size resolution of 2cm² when using a validated and calibrated pressure measuring system (Bus *et al.*, 2020).

The Fscan in-shoe measurement system is based on a resistive sensor technology. This relies on electric current flow between the sensors, with intensity linearly dependent on the amount pressure exerted on the sensor

(Giacomozzi & Vaclav, 2011). This is in contrast to a capacitive sensor system, such as the Pedar®-X (Novel GmbH, Munich, Germany).

4.19 Study Outcomes

Outcomes were developed to address the aims and objectives of the study:

- Assess the feasibility and acceptability of the trial procedures.
- Assess the appropriateness and performance of outcome measures and inform the sample size calculation of the anticipated future RCT.
- To explore the experiences of participants' receiving customised optimised insoles and Pulman-house shoe, or active control insole and Pulman-house shoe, and podiatrist's experiences of delivering the intervention.

All participants were invited to attend the baseline visit and three further assessment appointments for this study (Figure 4.5). These visits were in addition to the usual care monthly podiatry appointments. Although no recommended follow-up time points are specified in studies investigating DFU, this study's follow-up time points were selected as a safety net to provide checks on those with history of DFU, to minimise the established risk of DFU re-occurrence in the first year following healing (Armstrong, Boulton & Bus, 2017). Every effort was made to schedule assessments to synchronise with the participant's usual care podiatry appointment to minimise participant burden. To enable this a flex of two weeks either side of the relevant study time point was introduced.

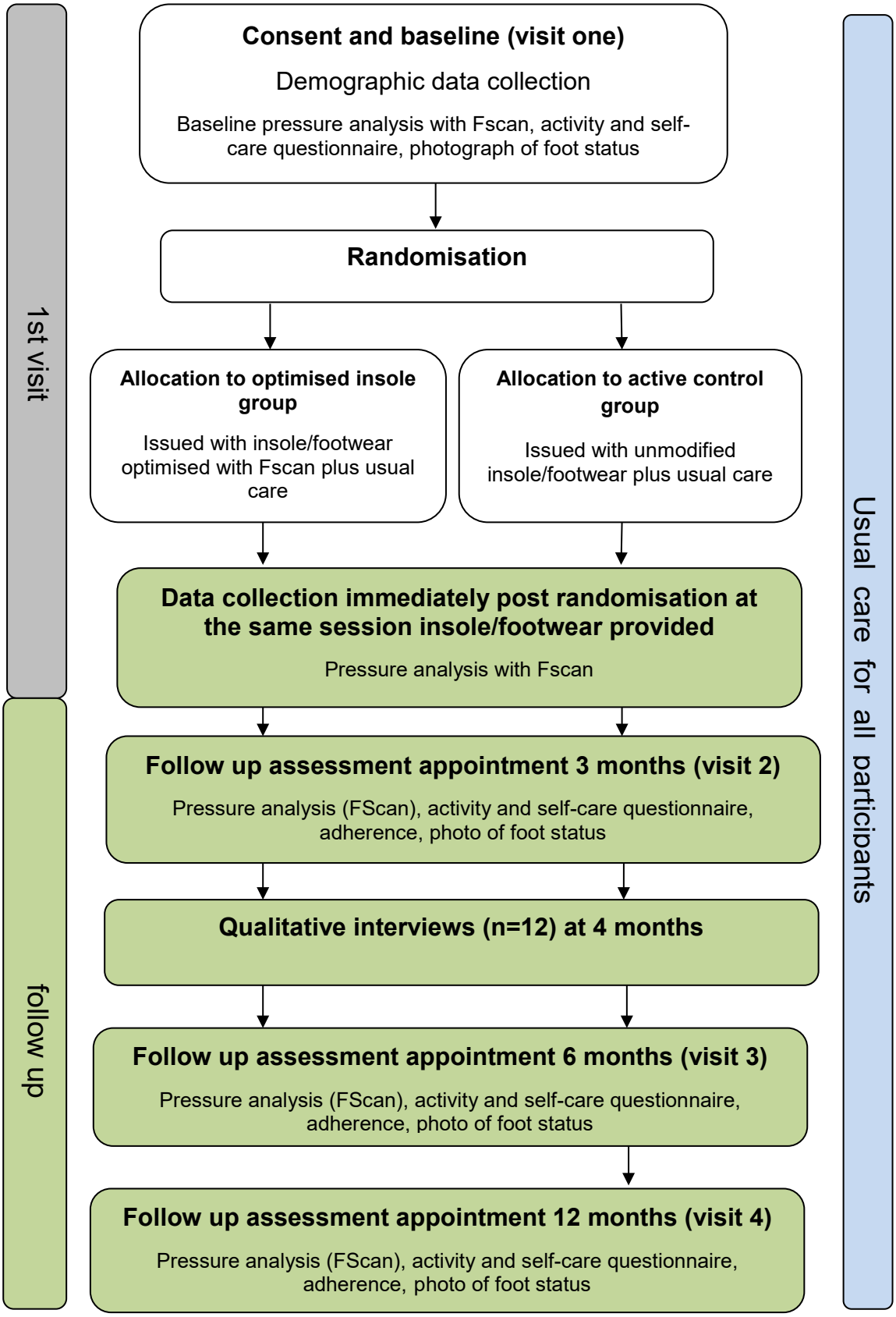


Figure 4.5 Participant flow chart

4.19.1 Primary outcomes

Objective one was to assess the feasibility and acceptability of the trial procedures. In particular:

- Recruitment and retention rates of eligible participants through the trial;
- The pragmatism of delivering the insole in the proposed settings;
- Variation and fidelity in the delivery of the insole;
- Intra-rater reliability of between session MPPP measures;
- The completeness of the data sets;
- The effectiveness of the blinding.

4.19.1.1 Recruitment and retention

As this is a feasibility study, the numbers of participants screened, eligible, randomised and withdrawn from the study were reported by study site and by group allocation (Boutron *et al.*, 2017; Eldridge *et al.*, 2016a). Reasons for exclusion and for withdrawal were summarised, where reported.

4.19.1.2 Pragmatism of delivering the insole

To monitor the adherence to delivery of the allocated insole, the number and type of protocol deviations were collected. After every participant visit, podiatrists were asked to complete a protocol deviation summary to document any unusual circumstances surrounding each intervention session. Completed protocol deviation summaries were sent to the PenCTU. The CI assessed the submitted protocol deviations.

4.19.1.3 Treatment fidelity

Treatment fidelity was assessed by podiatrists completing a self-reported fidelity checklist at the end of the session. Treatment fidelity refers to the extent to which core components of interventions are delivered as intended by the protocol procedures. They are included in trials of complex interventions to account for inferences made from study outcomes (Spillane *et al.*, 2007). Effective fidelity improves the validity of the results by assessing the extent to which an intervention is implemented as intended by its developers (Poltawski, Norris & Dean, 2014). Each fidelity checklist included items according to specific criteria to the process for delivering the footwear and insole intervention specified in the manual and protocol. Items were scored by yes/no answers. The checklist was piloted by one podiatrist and refinement made. The checklists, which were completed for a sample of 20% of participants for each site, were undertaken throughout the study period and sent to the PenCTU. The CI assessed the responses and missing data from each submitted checklist.

4.19.1.4 Intra-rater reliability of between session pressure measurement

To ensure consistency and repeatability in data collection in plantar pressure measurement, the intra-rater reliability of the MPPP measures was assessed. Intra-rater reliability of the MPPP measures was assessed by comparing the MPPP value between sessions for each podiatrist on the same participant. All of the tests were conducted on the same day to reduce burden on podiatrists and participants. Measurements of MPPP were collected in the morning and repeated four hours later on the same day. Intra-rater reliability was determined

using intraclass correlation coefficients (ICC's), the Standard Error of Measurement (SEM), and Bland-Altman plots (Bland & Altman, 1999; Koo & Li, 2016; Martin Bland & Altman, 1986; Weir, 2005). The ICC determined the relative reliability of the measures. The SEM provided an absolute index of reliability and an estimate of the precision of the scores to enable determination of the minimal differences needed to detect a true change in the outcome measure. In line with methods described by Weir (2005) this was determined by: SEM = SD √ 1-ICC. Bland Altman plots provided a visual display to compare the variability of each pair of measures using means and two standard deviations and determines the limits of agreement.

Several studies have evaluated the accuracy and reliability of pressure measurements using the Fscan in-shoe measurement system. One prospective study found that the system provided reliable measurements when assessing areas of high pressure and peak pressure for 51 participants with DM (Ahroni, Boyko & Forsberg, 1998). Participants were tested on two different days wearing their own shoes. A range of ICC's and coefficient of variations for different regions of the foot were reported ranging from fair-to-good to excellent reliability for heel, metatarsal head and hallux respectively. Another study reported adequate reliability when evaluating peak pressure measures taken from a mean of three steps over four separate sessions, although foot regions were not assessed (Mueller & Strube, 1996b). Compared to a force platform, the Fscan in-shoe system demonstrated no significant differences in the magnitude of the vertical component first peak force, minimum force, and the second peak force in a laboratory setting. However a significant delay in the temporal values of the same variables was reported (Chen & Bates, 2000).

Other authors have reported the limited accuracy of the Fscan in-shoe system sensor. In a bench-top test, the sensor was shown to have high errors of creep (19%), hysteresis (21%) and 10% variability across sensors (Woodburn & Helliwell, 1997). Despite these findings, the authors concluded that while the Fscan system has limited capability for absolute accuracy, it could be used for quantitative studies provided its limitations are noted. Confirming these limitations, Luo et al. (1998) performed a quantitative validation using a hydraulic system to test the Fscan sensor under different conditions (Luo, Berglund & An, 1998). They reported the sensor as adequate for determination of pressure distribution under contact conditions with soft materials, but was highly sensitive to temperature, loading speed and surface conditions. Nicolopoulos et al. (2000) examined several calibration methods of the Fscan system, and reported that accuracy of the outputs was highly dependent on calibration, hysteresis, preconditioning, bending, and shear loading and temperature (Nicolopoulos *et al.*, 2000).

To reduce the magnitude of error, calibration of the Fscan in-shoe system is advised prior to use, including surface contact conditions, loading speeds and temperature environment (Luo, Berglund & An, 1998). For example, intra-sensor variation was reduced from 31% to 15% by appropriate prior preparation (Koch, 1993). One experimental study tested a range of pressures loaded onto the sensor by a bladder system. They found that if pressure calibration was within the estimated range of applied pressure, measurement error was in the range 1%- 6%. When the calibration pressure was outside this range of applied pressure, measurement errors were considerably higher, ranging from -26.3 to 33.9% (Hsiao, Guan & Weatherly, 2002). A further experimental study involving

four participants compared the Fscan in-shoe system with a Kistler force plate, reporting high correlation coefficients (range 0.93- 0.99) in ground reaction force and stance time as a result of extended calibration (Ong & Wong, 2005).

In summary, the Fscan in-shoe measurement system has adequate to high reliability for quantitative measurements of plantar pressure. However, extensive calibration is needed to improve pressure measurement accuracy and reliability. Subsequently, a process for calibration of the Fscan according to the manufacturer's recommendations was constituted for this study.

4.19.1.5 The completeness of data sets/outcome measures

As this is a feasibility study, the levels of data completion and follow-up rates are important outcomes to identify areas for potential bias. All summaries were based on observations only and the number of missing observations for each characteristic were reported. The proportion of participants missing each outcome were summarised for each allocated group and at each time point, with reasons for missing outcomes documented wherever possible.

4.19.1.6 The effectiveness of the blinding

Blinding effectiveness was assessed using the Blinding Index (BI), a method for calculating the level of blinding success, irrespective of research area (Bang, Ni & Davis, 2004). Bang's BI is the proportion of unblinding in both group allocations, and can identify conflicting behaviours in different group allocations, including the 'wishful thinking' scenario (Park, Bang & Cañette, 2008). Wishful thinking is a form of bias whereby information is sought to confirm a belief, which can lead to misinterpretation. The BI considers these uncertain

responses from study participants in an appropriate way. The BI is based on responding to options regarding blinding to the insole allocation: ‘definitely sure’, ‘somewhat sure’, and ‘do not know.’

4.19.2 Secondary outcomes

Secondary outcome measures were related to the second objective; to select the most appropriate primary and secondary outcome measures to inform the sample size calculation of the anticipated future RCT by measuring:

- Incidence of plantar foot ulceration;
- Mean peak plantar pressure (MPPP);
- Nottingham Assessment of Functional Footcare questionnaire;
- International Physical Activity Questionnaire;
- Adherence to wearing the insole and footwear;
- Estimates of MPPP effect.

4.19.2.1.1 Incidence of plantar foot ulceration

Incidence of DFU (Oyibo *et al.*, 2001) has been suggested as the preferred primary outcome measure by expert opinion (Jeffcoate *et al.*, 2016). In this feasibility study, incidence of DFU was determined through combination of resources: collected from podiatrists, self-reported by participants and photographs of each foot demonstrating ROI on the plantar foot surface. The anonymised photographs were blindly assessed by the CI. The assessment of foot status by photograph has been shown to have good reliability and validity (Thompson *et al.*, 2013), although this is dependent on the quality of the images

produced. To safeguard the quality of the plantar foot images, a standard operating procedure incorporating distance, focus and lighting was provided.

4.19.2.1.2 Mean peak plantar pressure

MPPP is the mean of maximum pressure value of the sensors (of the in-shoe system) in a selected region of interest for a number of walking steps. Although there is no definitive MPPP threshold at which DFU occurs, elevated plantar foot pressure assessment is frequently used as a surrogate measure of DFU risk. Using dynamic in-shoe pressure measurement systems, MPPP can be calculated and assessed, where the magnitude of MPPP can indicate a perceived risk of DFU.

4.19.2.1.3 Nottingham Assessment of Functional Footcare questionnaire

The Nottingham Assessment of Functional Footcare questionnaire (Lincoln *et al.*, 2007) is a 29-item self-report questionnaire that was developed to assess the foot care behaviour of people with diabetes. It has demonstrated good test-retest reliability in people with diabetes (Lincoln *et al.*, 2007; Senussi, Lincoln & Jeffcoate, 2011). Evidence on foot self-care behaviours suggests that people with diabetes but without prior ulcers, and who examine their feet and check their shoes, are less likely to develop foot ulcers, but no clear association is evident for people with prior ulcers (Westby *et al.*, 2020). The ability to undertake and commit to foot care behaviours is associated with a reduction in DFU (Boulton, 2019).

4.19.2.1.4 International Physical Activity Questionnaire

The International Physical Activity Questionnaire short form (IPAQ-short) assessed physical activity levels at four intensity levels throughout the preceding seven-day week (Booth, 2000). Weight-bearing activity influences the amount of mechanical trauma in the plantar surface of foot, especially in those with DPN (van Deursen, 2004) and may be related to DFU occurrence (Westby *et al.*, 2020). It has excellent test–retest reliability (r= 0.75) over seven days (Craig *et al.*, 2003) and excellent reliability (r=0.77) over three days (van der Ploeg *et al.*, 2010). Advantages of the IPAQ-short are its brevity and provision of an overall total physical activity estimate. Limitations include an inability to detect changes in activity and although frequently used in diabetes studies, it was designed and tested only in healthy adults aged 18-69 years (Bauman *et al.*, 2009).

4.19.2.1.5 Adherence

Adherence to wearing the insole was assessed by a temperature sensor integrated into the optimised and active control insoles. The Orthotimer sensor (Rollerwerk Medical Engineering, Balingen, Germany) is embedded in a small (13mm × 9mm × 5 mm), dust-tight and watertight unit. It is powered with a lithium dry cell battery (3.0 V/5.5 mAh) with a lifespan of at least 18 months. It records time, date, and temperature every 15 min and has 400 days of storage capacity. The sensor has a temperature precision of ± 0.1°C. The sensor's data was collected by the podiatrist at each follow-up appointment with a wireless reading device via Radio Frequency Identification (RFID) technology (ISO 15693) and transferred to the accompanying software. The reading device and

computer were connected via a USB plug. The sensor, reader, and software have certification marking (CE Class 1, MDD 2007/47 /CE). The CI was responsible for analysing the uploaded data.

Traditionally, adherence to footwear interventions is quantified by subjective methods. This is often using self-reported diaries or questionnaires (Chantelau & Haage, 1994a; Chantelau, Kushner & Spraul, 1990; Paton *et al.*, 2012; van Netten *et al.*, 2010). Subjective methods of adherence assessment are known to have poorer reliability. Patients tend to underreport non-adherence to avoid dissatisfaction from their healthcare provider (Vik, Maxwell & Hogan, 2004). One study suggested under reporting of subjective compliance by 150% when compared to an objective measure when wearing a spinal brace (Nicholson *et al.*, 2003). Non-adherence can increase variance, lower study power, and reduce the magnitude of treatment effects (Shiovitz *et al.*, 2016). This is particularly pertinent in people at risk of DFU, where review studies have depicted the under-adherence of wearing footwear and insoles prescribed for offloading (Bus *et al.*, 2008; Bus *et al.*, 2016; van Netten *et al.*, 2016).

A more objective approach for measuring adherence is the use of a temperature-based system. Previous studies have used a temperature sensor placed in the footwear or insole to assess the use and non-use of the prescribed devices. Good validity was reported using a temperature monitor system over a seven day period (Bus, Waaijman & Nollet, 2012; Waaijman *et al.*, 2013). Similarly, a high correlation ($r=0.995$, $p<0.001$) was determined for wearing orthopaedic footwear when using the Orthotimer system, compared to a standard camera reference over a 48 hour period (Lutjeboer *et al.*, 2018).

Another study reported the ability to discriminate long term patterns of use of diabetic footwear for 26 participants over a continuous mean of 133.5 days using the Orthotimer temperature sensor system (Ehrmann *et al.*, 2017).

4.19.2.1.6 Estimates of effect

Appropriate confidence intervals of the mean, standard deviation of MPPP and the correlation between baseline and follow-up MPPP measures were calculated to inform a power calculation for sample size estimate for the anticipated RCT.

4.20 Embedded qualitative study

The aim of the qualitative component was to explore the experiences of participants' receiving customised optimised insoles and Pulman-house shoe, or active control insole and Pulman-house shoe, and the podiatrists' experiences of delivering the intervention. This related to objective three of the feasibility study and will inform the design of the anticipated RCT. The concept of an embedded qualitative component in a feasibility RCT and its contribution to the results and findings is widely accepted in the literature (see Chapter four, section 4.2 and 4.4).

4.20.1 Design

This study used a qualitative method design embedded within the feasibility RCT. Semi-structured interviews (Kallio *et al.*, 2016) were conducted with study participants and podiatrists. Semi-structured interviewing provides a clear set of open-ended questions to follow relevant topics, but still provides the opportunity

for the interviewer to modify the sequence and wording according to context (Peters & Halcomb, 2015; Whiting, 2008).

4.20.2 Sampling and participants

A purposive sampling approach was used. Twelve patient participants, four from each study site, and three podiatrists from the three study sites delivering the intervention were selected for participation. Purposive sampling enables the identification and selection of information-rich cases related to the phenomenon of interest (Palinkas *et al.*, 2015; Patton, 1990). Critics of this approach highlight that participants are not randomly selected introducing bias (Etikan, Musa & Alkassim, 2016). A sampling matrix was created to achieve maximum variation in previous foot ulcer history, gender, age, and treatment intervention to explore a diverse population of participants' experiences. Patient participants were approached by the podiatrist at their scheduled three-month follow-up visit and were invited to become involved in the embedded qualitative study. Interviews were timed to capture participants' experiences of receiving the intervention and the follow-up process, before their experiences were forgotten with time. Podiatrists were contacted by the CI six months following the onset of the feasibility trial.

All potential patient participants and podiatrists indicating their willingness to be interviewed received a PIS specifically relating to this qualitative component of the feasibility trial. At least 24 hours were given for them to consider their participation before being contacted by the site PI or the CI to check their continued interest in participating and answer any questions. The CI acquired written consent before the interview.

4.20.3 Data collection

Interview schedules were prepared by the study team to guide the interview and explore relevant issues to the participants' experiences of the trial intervention. The focus was on achieving depth of responses within the context of receiving the intervention, but not limiting the breadth of the answers. The CI, who conducted all interviews, used prompts and encouraged patient participants and podiatrists to expand on their initial responses and followed up on ideas that the interviewees raised themselves. The interviews for patient participants took place either at their home or a quiet room in the hospital, depending on their preference. Interviews of the podiatrists took place privately in a quiet clinical room. Before the start of the interviews, the CI introduced himself and gave a brief explanation of the reason for undertaking the interview. The CI then asked the patient participants and podiatrists to speak freely as he was interested in hearing what they had to say, emphasising that there were no right or wrong answers. Verbal instructions were provided, indicating that the interview would be tape-recorded and then transcribed at a later date.

Interviews lasted between 25 and 45 minutes, ending when no further ideas emerged and the patient participants and podiatrists had reached saturation to the questions and prompts (Kerr, Nixon & Wild, 2010). The interviewing was iterative to strengthen the data gathering process (Smith & Firth, 2011). After reviewing the first three patient participant interviews, the interview schedule was adjusted by the study team to incorporate new topics that had emerged.

4.20.4 Qualitative analysis

Thematic analysis based on the six steps of Braun and Clarke was utilised to investigate the data (Braun & Clarke, 2006). Thematic analysis, as part of an ethnological methodology, is an independent qualitative descriptive approach and is mainly described as “a method for identifying, analysing and reporting patterns (themes) within data” (Braun & Clarke, 2006). The emphasis on exploring the essence of the groups’ experiences and the shared patterns and behaviours within that group (Reeves, Kuper & Hodges, 2008) suited the aims of this research.

The first step included the transcription of the interviews verbatim by the CI, during which the writing down of initial thoughts and ideas as part of the process occurred. The transcribed data was then read and re-read alongside the recordings to ensure the accuracy of the transcription. This process of repeated reading can assist in data immersion and refers to the researchers’ closeness to the data (Braun & Clarke, 2006).

In the second step, two researchers, RC and LTW, independently coded the transcribed data. The qualitative data analysis software NVivo (v12.0) was used to facilitate the organization and structuring of the process of coding and categorization and the development of relationships among concepts. The coding process identified sub-themes that the researchers considered pertinent to the essence of the experiences of the patient participants and podiatrists. Constant comparison was used to ensure that the thematic analysis represented all perspectives.

RC is the CI and a podiatrist. LTW is an Occupational Therapist and was selected to provide a viewpoint outside of the podiatry specific profession to add independence to the coding process. Describing the relationship that a researcher has in the context of the study provides integrity to the findings and extends the understanding of the work (Dodgson, 2019). Recognising reflexive position allows self-evaluation and the effect that it may have on the setting and people being studied (Berger, 2015). As such, reflexivity acknowledges that findings are created based on researcher's assumptions, rather than objective analysis. Using independent researchers with diverse reflexive traits, can uncover multiple meanings in a text during analysis (Green *et al.*, 2007) and can augment rigour and trustworthiness within qualitative research (Creswell & Poth, 2016).

In the third step thematic maps were created to enable visualisation of the links and relationships between codes and sub-themes (Braun & Clarke, 2006). Any codes that were too diverse or not supported by sufficient data were discarded. Castleberry and Nolan (2018) term this process as re-assembling and discuss the value of a visual tool to articulate how themes are subordinate or superordinate to each other (Castleberry & Nolen, 2018). The authors suggest that by clustering similar codes, the researcher is able to analyse the hierarchical data at multiple levels, which enables an appreciation of the data over the whole landscape. This provides a structured approach to reduce the qualitative data, as well as communicates relationships between codes and sub-themes. Potential themes are then extracted.

Step four encompassed checking and re-coding to ensure the completeness and appropriateness of the data and the potential themes. This step considered

the codes and sub-themes in relation to the objective; experiences of patient participants' receiving the insole allocation, and podiatrists' experiences of delivering the intervention. Additionally, strategies of peer debriefing for the CI by the third researcher (JML) and member checking with the PPI representatives were used to interpretatively validate the respondent statements.

Step five involved identifying and preparing a descriptor of the themes. Describing each theme aided in differentiating it from codes and sub-themes, giving depth to its role as a concept (Vaismoradi *et al.*, 2016). Undertaking this step helped to identify thematic patterns across the data and relationships between themes. However, Yin (2015) provides caution that researchers should still return to the data and coding process, as analysis should be a cyclic and not linear process (Yin, 2015). This was the approach taken in this study.

Stage six related to selecting the narratives of the transcripts to illustrate elements of the themes. Themes were used to interpret relationships and global findings from other themes and sub-themes. This stage is cited as the interpretative step whereby analytical conclusions are drawn from the data and presented in the findings (Castleberry & Nolen, 2018). Creating a logical narrative to describe and evaluate the findings helps the reader to decide for themselves whether the story is a legitimate research endeavour (Koch, 1998). However, caution must be exercised that the findings tell the story of the data, and not that the data supports the researchers' theory (Anderson, 2010).

4.21 Statistics and quantitative data analysis

For this feasibility study, the CI was responsible for data analysis, supported by the study statistician. A comprehensive Statistical Analysis Plan (SAP) was drafted prior to the final database lock and agreed by the TSC. As per the CONSORT extension for feasibility and pilot trials (Eldridge *et al.*, 2016a), the analyses assessed the acceptability and feasibility of the optimised insole in comparison with the active control insole, to allow assessment against progression criteria and provide data to inform a sample size and resources required for a future definitive RCT.

The CI and study statistician were blinded to group allocation while conducting the main analyses. Datasets were provided with codes for group allocation without specifying which group was which. Statistical analyses were undertaken using Statistical Package for the Social Sciences (SPSS) version 25 (IBM Corporation, Released 2016), supplemented where required by StataSE Version 14.0 and R (www.r-project.org).

Statistical analyses were undertaken once the final participant had completed the final study assessment at 12 months post-randomisation, the database was locked, the data cleaned and prepared for analysis. As far as possible (allowing for the possibility of missing data), all primary analyses were based on the intention-to-treat principle. The participants were analysed according to the group to which they were randomised.

Baseline demographic and clinical data were summarised for the intention to treat population, for each of the two allocation groups. Continuous variables

were summarised as mean (standard deviation) and median (interquartile range) whilst categorical variables were summarized as frequency and percentage. Graphical displays of histograms were used to examine the data distribution.

As this was a feasibility study and not powered to detect effectiveness, no formal testing for any of the summary measures was undertaken whilst comparing the variables between the group allocations. However, recent guidance from the NIHR suggests a 'signal of efficacy' should be reported. The purpose of the signal of efficacy is to indicate at an early stage whether an intervention is desirable to continue to full testing, rather than wasting valuable resources (Brown, Chuang-Stein & Kirby, 2012). However, detecting any effects in a small feasibility study will increase the probability of false positive and false negative errors (Rubinstein *et al.*, 2005).

Consequently, the between-group differences of the change in MPPP and correlation co-efficient from baseline to each follow-up time-point were calculated to provide an estimate of a signal of efficacy. The mean of all ROI's were calculated both unadjusted and adjusted for baseline plantar pressure (to account for possible regression to the mean) using analysis of covariance (Linden, 2013). All estimates of effect were accompanied by 95% confidence intervals, which gave directions and strength of effect (Shakespeare *et al.*, 2001).

4.21.1 Sample size calculation

An important objective of feasibility studies is to gather the necessary data to enable the calculation of a sample size for the anticipated main study.

Appropriate sample size is vital to ensure that any difference between the comparator groups in a study is correctly assessed. Whitely and Ball (2002) suggest that whilst sample size calculations are subjective, combining power, effect size and probability value will determine an appropriate size (Whitley & Ball, 2002). Good sample size estimates will include information from similar studies in comparable populations or from an appropriate feasibility study.

Estimates from the data collected in this feasibility trial were used to inform potential sample size calculations for a main RCT. In particular, the estimates of MPPP confidence intervals and correlations between baseline and follow-up time points for both group allocations provided sample size calculations based on varying assumptions/scenarios.

4.22 Study oversite

This study had a trial steering committee (TSC) and a trial management group (TMG). The TSC was chaired by an Endocrinology Consultant (independent) and consisted of an independent lay member, an external statistician (independent), study sponsor and three other experienced trialists, one of whom was independent. This met on four occasions. The TMG was chaired by the CI and included the PenCTU's trial and data manager, trial statistician, patient representative and the CI's PhD supervisors. This met on a monthly basis to monitor the study progress and discuss and problem solve issues as they arose.

All study procedures were overseen by the CI and conducted in compliance with the study protocol, according to the principles of Good Clinical Practice (GCP).

Deviations from (or non-compliance with) the approved protocol were recorded on study-specific non-compliance reporting forms and reviewed for action by the CI. All investigators and study site staff complied with the requirements of the Data Protection Act 1998 and GDPR 2018 with regards to the collection, storage, processing and disclosure of personal information and upheld the Act's core principles.

Throughout the study, all possible precautions were taken to ensure participant safety and wellbeing. Adverse Event (AE) and Serious Adverse Events (SAE) were recorded, and investigated to ascertain their relationship to the trial intervention. AE's and SAE's were regularly reviewed by the TMG. SAE's were reviewed by the TSC.

4.23 Public and patient involvement

This study was informed by people with DPN and at risk of DFU. Involving patients and the public (PPI) is central to improving the quality and relevance of research (Hoddinott *et al.*, 2018). Although there is no explicit framework to determine the role of PPI within the context of a study, INVOLVE, a national advisory group that supports greater public involvement in NHS, public health and social care research, provides information and resources to help shape this (National Institute of Health Research, NIHR, 2019b) .

4.23.1 Patient and participant involvement in research design

A patient advisory group was formed at the University of Plymouth consisting of participants who had been involved in the initial proof-of-concept pilot study (refer to Chapter 3, section 3.1). The group reflected on their personal

experiences of being participants, both positive and negative, and their experiences were used to help formulate the specific focus and subsequent design of this feasibility study. In particular the Pulman-house-shoe and the use of an RCT design was deemed acceptable, although the concept of receiving no insole left some bewildered. The introduction of the active control insole helped to satisfy these concerns. The length of the initial podiatry appointment to receive the insole intervention was discussed and the advocates felt that this was acceptable. The short study name, INSTEP (Insoles To Ease Pressure), originated from one of the patients.

4.23.2 Patient and participant involvement in trial management

The TMG and TSC included public and patient representatives to enable ongoing input to the study and management of the research from a patient perspective. The development of study documentation involved PPI representation to enhance readability. The PIS's and insole leaflets were reviewed and scrutinised for their suitability and understanding for people with DPN. Throughout the study, the PPI representatives contributed to the study management, suggesting strategies for improving recruitment and retention of participants to the study. The representatives worked collaboratively with the CI on developing the interview schedules, PIS and consent forms for the qualitative component of the study. Further, the TMG representative checked the themes and sub-themes as part of the thematic analysis.

4.24 Determining progression to full study

Pre-specified criteria for the feasibility of progression to a main study is

recommended for pilot and feasibility studies (Mbuagbaw *et al.*, 2019). This enables transparency and provides focus to the study objectives. Pre-specification of criteria took the form of a 'traffic-light approach', as opposed to a 'start-stop' method (Avery *et al.*, 2017). These criteria were determined from synthesis of previous diabetic foot offloading studies and pragmatic feasibility studies (Table 4.1). This research will progress to a full trial application if minimum success criteria are achieved in key feasibility aims and objectives, and/or if solutions to overcome any issues can be identified.

Table 4.1 Criteria for trial progression

	Criteria	Scenario 1	Scenario 2	Scenario 3
1	% of recruitment target achieved (76 participants)	≥70%	51-69%	≤50%
2	% of participants completing 3,6 and12 months follow up	≥80% of the target figure	51-79% of the target figure	≤50% of the target figure
3	% of outcome measures completed for those attending the assessments	≥80% of the target figure	61-79% of the target figure	≤60% of the target figure
	Proposed action	Proceed to submitting plan to funder for full trial	Discuss with TSC and funder about progression and resources needed to achieve target	No progression to plan a full trial in the current design

4.25 Chapter summary

This chapter has presented the rationale and method for the INSTEP feasibility RCT with embedded qualitative study. Justification of the philosophical approach and how this methodology can best answer the study aims and objectives was provided. The strength of this feasibility study is using a RCT design with embedded qualitative study, which is the proposed design for the anticipated main trial. The feasibility design pragmatically tested the operational parameters to inform the development of an anticipated large scale RCT to assess the clinical and cost effectiveness of the optimised insole in reducing the risk of DFU. Subsequently, the quantitative results from the INSTEP study are provided in Chapter 5 and the findings of the qualitative component in Chapter 6.

Chapter 5 Quantitative results of the feasibility RCT

In the previous chapter, justification for the chosen research approach and methodology for the INSTEP feasibility study was described. This chapter presents the quantitative results in line with the objectives of this study. A statistical analysis plan (SAP) formed the roadmap for analysing the results agreed to *a priori* by the independent Trial Steering Committee. The SAP was formulated following the CONSORT extension for Pilot and Feasibility Studies (Eldridge *et al.*, 2016a) also being cognisant of the CONSORT extensions for reporting participant-reported outcomes (Calvert *et al.*, 2013) and non-pharmacologic treatment interventions (Boutron *et al.*, 2017).

In line with the recommendations for a feasibility trial, no power calculation was undertaken. Data are presented with descriptive statistics and, while comparing variables between the treatment groups, no hypothesis testing was undertaken. Continuous variables are presented as mean (standard deviation), median (interquartile range) and their distribution are assessed by visual evaluation of histograms. Categorical variables are summarised by frequency and percentage, with percentages being rounded to one decimal place.

5.1 Objective 1: Assess the feasibility and acceptability of trial procedures

Objective one (see Chapter 4, section 4.19.1) was to assess the feasibility and acceptability of the trial procedures. In particular, this objective evaluated the following outcomes:

5.1.1 The proportion of eligible patients recruited

The opening of participant recruitment to the study varied across the three participating sites. The Solent site opened recruitment in November 2017; Torbay in December 2017, and Exeter in January 2018. Recruitment closed for all sites on December 31st, 2018. All interventions and research assessments were completed by the end of January 2020.

In total, 142 potentially eligible patients were screened and received a patient information sheet (Table 5.1). After screening, 57.0% (n=81/142) were not considered for further participation in the study (Table 5.1). Forty-three percent (n=61/142) of the target population were recruited and randomised to the active control insole group (n=31) or optimised insole group (n=30) (Table 5.1).

Table 5.1 Number of patients screened from the target population and recruited to study by site

	Torbay (n)	Solent (n)	Exeter (n)	Total (n)
Screened	53	43	46	142
Not eligible	2	12	10	24
Not recruited	18	22	17	57
Total randomised	33	9	19	61
Proportion randomised/potentially eligible	62.3%	20.9%	41.3%	43.0%

Sixty-one participants, out of the initial recruitment target of 76, were recruited within the 13 months' timescale, with variation in performance by site (Figure 5.1). Torbay over-recruited to their target (n=33); Solent (n=9) and Exeter (n=19) both under-recruited to their target. The highest recruiting site, Torbay,

was the host site for the CI. The recruitment rate was 4.4 participants per month across all sites. This rate was less than the recruitment rate of two participants per site per month agreed by all sites at the study's outset.

The participant flow diagram is presented in figure 5.2. In line with CONSORT recommendations (Moher *et al.*, 2010), this includes information related to the reporting of pragmatic trials.

Figure 5.1 Actual versus target recruitment rate for the INSTEP study by site

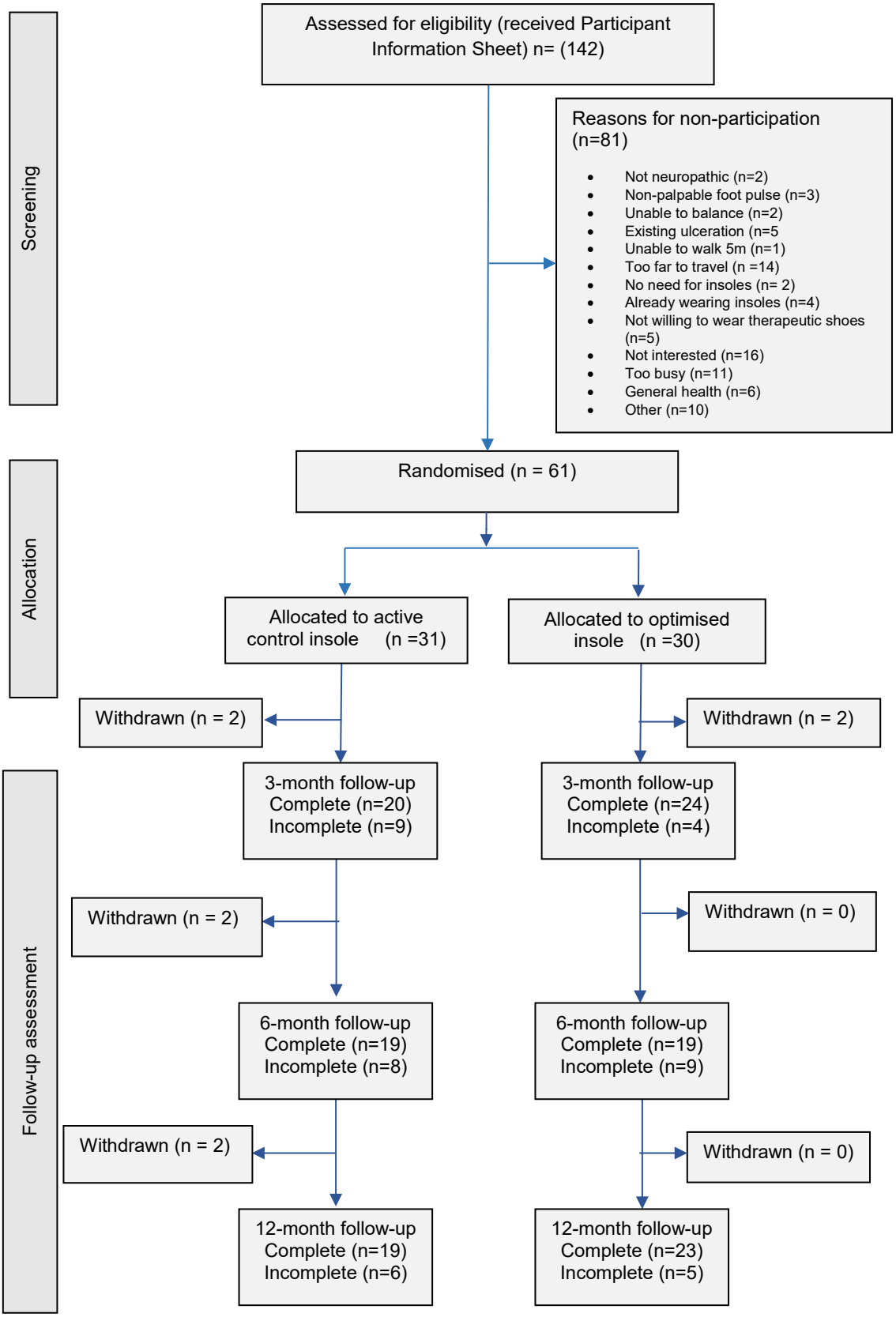


Figure 5.2 Consort of participant flow through study

5.1.2 Retention rates of participants through the trial

There was variability in the number of participants completing the study follow-up visits at three, six, and 12-months post-baseline. At three-month follow-up, 72.1% (n=44/61) of randomised participants completed the study appointment, decreasing to 62.3% (n=38/61) at the six-month follow-up time point. At 12-months follow-up, 68.9% of all participants (n=42/61) completed the study follow-up. The active control insole group had proportions of participants completing the study of 64.5% (n=20/31) at three-months and 61.3% (n=19/31) at both six and 12-months follow-up time points. This compared to proportions of participants from the optimised insole group completing the study of 80.0% (n=24/30), 63.3% (n=19/30) and 76.6% (n=23/30) at three, six and 12-months respectively.

5.1.2.1 Withdrawal and loss to follow-up

At 12-months post randomisation, 33.1% (n=19/61) of participants were lost to follow-up with 13.1% (n=8/61) specifying reasons. These were: moving out of the area (n=3), death (n=1), ongoing foot ulceration (n=1), study too burdensome (n=1), ill-health (n=1), no reason (n=1). The proportion of participant withdrawals for each site were 36.8% (n=7/19) at Exeter, 33.3% (n=11/33) at Torbay and 11.1% (n=1/9) at Solent.

5.1.3 Assessing the pragmatism of delivering the insole intervention

The evaluation of protocol deviations informs the pragmatism of delivery of the insole intervention at the sites. The proportion of participants with protocol

deviations was 24.6% (n=15/61), varying from 21.2% (n=7/33) for Torbay, 21.0% (4/19) for Exeter and 44.4% (4/9) for Solent.

There were 19.7% (n=12/61) of the deviations related to clinical delivery and operational constraints at each site; the wrong sized Pulman-house-shoes for one participant and clinical capacity issues for booking appointments (n=11). There were 4.9% (n=3/61) of protocol deviations related to patient factors; loss of insole with data logger (n=1) and patients not attending follow-up appointments within the allotted time-frame (n=2).

5.1.4 Variation and fidelity in the delivery of the intervention

The self-completion of a fidelity checklist measured the variation and fidelity of adherence to the standardised protocol for delivering the intervention by the podiatrists at each site. A total of 32.8% of checklists (n=20/61) were completed exceeding the target of a 20% completion rate. This was due to Torbay and Exeter sites initially completing checklists for all participants. Checklist completions by site were: Torbay 50.0% (n=10/20), Solent 20.0% (n=4/20), Exeter 30.0% (n=6/20).

Full adherence was reported in 90.0% (n=18/20) of the self-reported checklists. Omissions (n=2) relating to failure to handing out the documentation on aftercare advice to the participant occurred at two sites. Both omissions were corrected retrospectively by the podiatrists at each site as soon as the omission was identified.

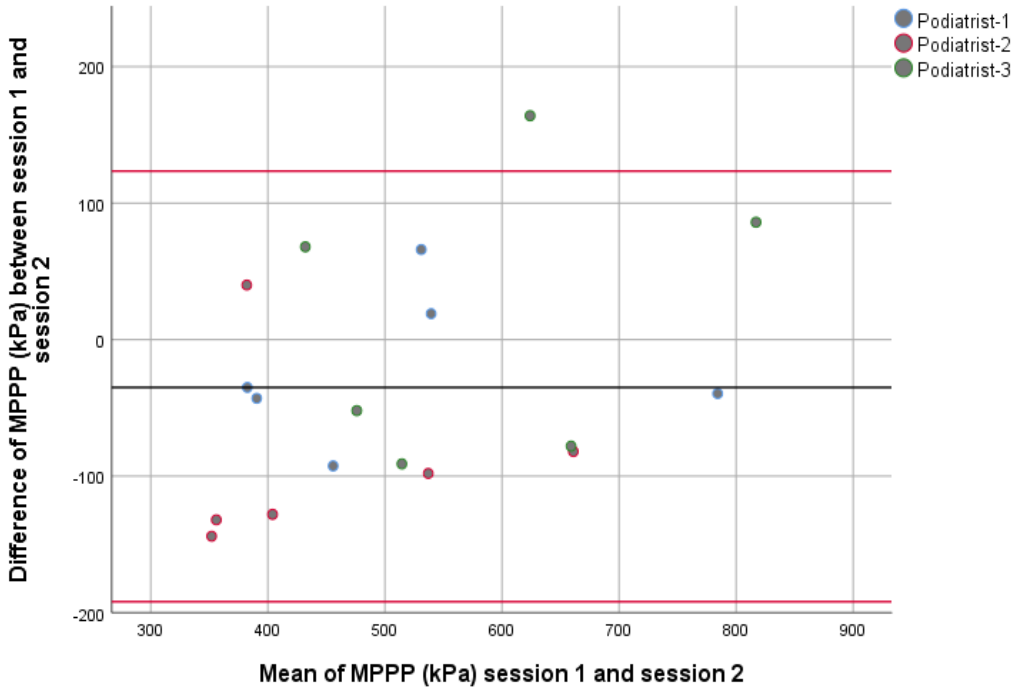
5.1.5 Intra-rater reliability of plantar pressure measurements

Evaluation of the intra-rater reliability of plantar pressure measurements between sessions was by comparing the MPPP value for each podiatrist. The podiatrists from each site (n=3) collected MPPP for the region of interest-1 for the same participants (n=6) in the morning session. They repeated the test with the same participants in the afternoon. Using a two-way random-effects model with absolute agreement (Koo & Li, 2016), the intra-class correlation coefficient ranged from 0.83 to 0.97 for the podiatrists (Table 5.2). Standard error of measurements ranged from 23.9 to 48.0 (Table 5.2). Visual examination of the Bland Altman plot (Figure 5.3) shows all but one plot lay within the limits of agreement, indicating satisfactory agreement between pressure measurement sessions (Bland & Altman, 1999).

Table 5.2 Intra-class correlation coefficients and standard error of measurements for the podiatrists

	Podiatrist 1	**Podiatrist 2**	**Podiatrist 3**
ICC (95%CI)	0.97(0.80-0.99)	0.83 (-0.22-0.98)	0.88 (0.10-0.98)
SEM (95%CI)	23.9 (-23.0-70.7)	52.0 (–49.9-153.9)	48.0 (-46.08-142.1)

ICC- intra-class correlation coefficient, CI-confidence intervals, SEM-standard error of measurement



The differences between the MPPP measurements for session 1 and session 2 are plotted against the mean of the MPPP measurements for sessions 1 and 2 for the three podiatrists. Lines are plotted indicating the mean (black) and limits of agreement (± 1.96 sd) (red).

Figure 5.3 Bland-Altman plot of intra-rater pressure measurement

5.1.6 The proportion of completed data sets

An assessment of the proportion of completed data sets was undertaken for MPPP, photographs and baseline variables.

5.1.6.1 Mean peak plantar pressure and photographs

There was minimal variation in the proportion of completed data sets between the optimised insole group and active control insole group, and no missing data for MPPP and photographs for those who attended the follow-up sessions.

At three months follow-up, 72.1% (n=44/61) of MPPP measurements and uploaded photographs assessing foot ulcer status were collected. At six-months, 60.7% (n=37/61) and at 12-months follow-up, 67.2% (n=41/61) of MPPP data sets were collected. One participant stopped using the insole intervention due to problems with wearing the Pulman-house shoes before the six months follow-up. No MPPP data was collected at the six-months and 12-month follow-up for this participant. However, they completed all of the remaining study assessment procedures and are included in the analysis. At six-months 62.2% (n=38/61) and at 12-months follow-up 68.9% of photograph data sets (n=42/61) were obtained.

5.1.6.2 Baseline variables

There was a completion rate of 98.3% (n=60/61) for all baseline data sets. Baseline variables were collected for both groups and summarised for demographics, significant medical history, and clinical variables.

5.1.6.2.1 Demographic data

The demographic data at baseline are presented in Table 5.3. There were similar proportions of participants with medical conditions between the active control insole and optimised insole group. The age range for the active control insole group was 32-86 years (mean 67.9 years), and the range for the optimised insole group was 40-88 years (mean 70.2 years). Overall there were more males, 86.9% (n=53/61) than females, but both groups were similar in composition in this respect with 83.9% males (n=26/31) in the active control insole group and 90.0% (n=27/30) in the optimised insole group. All participants were white.

Table 5.3 Demographics by treatment group allocation

		Active control insole group n=31	Optimised insole group n=30
Age (years)	Mean (SD)	67.9 (12.2)	70.2 (10.2)
	Median (IQR)	70.0 (60.0-73.0)	71.5 (67.6-74.8)
Gender, n (%)	Female	5 (16.1%)	3 (10.0%)
	Male	26 (83.9%)	27 (90.0%)
Height (cm)	Mean (SD)	177.2 (11.0)	176.1 (9.1)
	Median (IQR)	178.0 (171.5-183.5)	177.0 (171.0-183.0)
Weight (kg)	Mean (SD)	95.0 (14.1)	94.4 (18.6)
	Median (IQR)	94.0 (85.0-107.0)	92.0 (79.6-111.3)
BMI (kg/m^2)	Mean (SD)	30.4 (4.6)	30.4 (5.5)
	Median (IQR)	29.8 (37.7-32.2)	29.5 (20.3-35.8)
Ethnicity, n (%)	White	31 (100%)	30 (100%)
Smoker, n (%)	Yes	3 (9.7%)	2 (6.7%)
	No	28 (90.3%)	27 (90.0%)
	Missing	0 (0)	1 (3.3%)
Diabetes type, n (%)	Type 1	7 (22.6%)	2 (6.7%)
	Type 2	24 (77.4%)	28 (93.3%)
Duration of diabetes (years)	Mean (SD)	21.3 (9.7)	19.7 (14.9)
	Median (IQR)	20 (14.5-27.5)	17 (6.0-28.5)

% expressed as a proportion of group allocation, SD-standard deviation, IQR-Interquartile range, n-number, cm-centimetre, BMI-body mass index, kg-kilogram, m-metre

5.1.6.2.2 Medical history

The medical history variables for participants at baseline are summarised in Table 5.4. These medical conditions are considered for their relevance to diabetes and the risk of DFU. There were similar proportions of participants with medical conditions between the active control insole and optimised insole group. Blood sugar levels and kidney function were comparable between these groups, as indicated by the HbA1c and eGRF values.

Table 5.4 Medical history by treatment group allocation

		Active control insole group n=31	Optimised insole group n=30
Inflammatory arthritis, n (%)		2 (6.5%)	2 (6.7%)
Cardiovascular disease, n (%)		13 (41.9%)	11 (36.7%)
Renal disease, n (%)		7 (22.6%)	4 (13.3%)
Respiratory disease, n (%)		7 (22.6%)	5 (16.7%)
Gastro-intestinal tract, n (%)		4 (12.9%)	6 (20.0%)
Central Nervous System, n (%)		4 (12.9%)	2 (6.7%)
Other co-morbidities, n (%)		10 (32.3%)	6 (20.0%)
Vision status, n (%)	Near acuity	29 (93.5%)	30 (100%)
	Distant acuity	30 (96.7%)	30 (100%)
HbA1c (mmol/mol)	Mean (SD)	64.8 (25.6)	59.7 (19.3)
	Median (IQR)	61.0 (49.0-72.0)	60.0 (50.0-73.5)
eGFR (mL/min)	Mean (SD)	64.6 (22.8)	64.1 (23.2)
	Median (IQR)	68.0 (51.0-84.0)	69.0 (45.0-85.5)

% expressed as a proportion of group allocation, HbA1c- glycated haemoglobin, mmol/mol - millimoles per mole, eGFR- estimated glomerular filtration rate, mL/min – millilitres per minute

5.1.6.2.3 Clinical variables

Participant anthropometric measures were collected at baseline using clinician rated and validated clinical measures (foot posture index FP-6 (Keenan *et al.*, 2007), ankle joint (Bennell *et al.*, 1998), sub-talar joint (Elveru *et al.*, 1988), first metatarsal phalangeal joint range-of-motion (Vulcano, Tracey & Myerson, 2016) and clinician rated balance status (Romberg's test) (Khasnis & Gokula, 2003). These measures demonstrated minimal variation between the active control insole and optimised insole group (Table 5.5) apart from prominent metatarsal heads. The active control insole group had 41.9% (n=13/31) of participants with prominent metatarsal heads compared to the 23.3% (n=7/30) in the optimised insole group. There were similar proportions of participants with a history of previous foot ulceration in each group: active control insole group 51.6% (n=16); 50.0% (n=15). No participants had existing foot ulceration.

Table 5.5 Clinical variables by treatment group allocation

		Active control insole group (n=31)	**Optimised insole group (n=30)**
1st MTPJ left foot dorsiflexion (degrees)	Mean (SD)	57.2 (26.6)	54.3 (22.5)
	Median (IQR)	55.0 (45.0-80.0)	50.0 (40.0-68.8)
1st MTPJ right foot dorsiflexion (degrees)	Mean (SD)	52.6 (28.4)	53.6 (21.7)
	Median (IQR)	50.0 (30.0-67.0)	55.0 (40.0-70.0)
Ankle dorsiflexion left foot (cms)	Mean (SD)	5.4 (3.5)	4.9 (4.2)
	Median (IQR)	5.0 (2.0-9.0)	5.0 (0-9.0)
Ankle dorsiflexion right foot (cms)	Mean (SD)	5.8 (3.3)	4.5 (3.9)
	Median (IQR)	5.0 (4-9.0)	4.0 (0-8.0)

(Table 5.5 Continued)		Active control insole group (n=31)	Optimised insole group (n=30)
STJ inversion left foot (degrees)	Mean (SD)	11.8 (5.9)	12.9 (5.6)
	Median (IQR)	10.0 (10.0-15.0)	10.0 (10-15.8)
STJ inversion right foot (degrees)	Mean (SD)	11.1 (6.9)	11.9 (6.5)
	Median (IQR)	10.0 (5.0-15.0)	10.0 (8.5-16.3)
STJ eversion left foot (degrees)	Mean (SD)	5.0 (3.6)	4.1 (2.9)
	Median (IQR)	5.0 (5.0-7.0)	5.0 (1.5-5)
STJ eversion right foot (degrees)	Mean (SD)	5.3 (4.4)	4.4 (3.6)
	Median (IQR)	5.0 (2.0-8.0)	5.0 (0-5.5)
FPI index left	Mean (SD)	1.2 (3.7)	1.9 (5.2)
	Median (IQR)	0.5 (-1.8-4)	1.5 (-1.3-6.3)
FPI index right	Mean (SD)	1.2 (4.7)	1.6 (5.8)
	Median (IQR)	1.0 (-2-5.5)	0.5 (-1.3-6.5)
Left foot deformity			
Claw toes n (%)		18 (58.1%)	17 (56.7%)
HAV n (%)		8 (25.8%)	11 (36.7%)
Plantarflexed 1st ray n (%)		16 (51.6%)	15 (50.0%)
Prominent met heads n (%)		13 (41.9%)	7 (23.3%)
Loss of fatty pad n (%)		18 (58.1%)	13 (43.3%)
Oedema n (%)		4 (12.0%)	5 (16.7%)
Right foot deformity			
Claw toes n (%)		18 (58.1%)	17 (56.7%)
HAV n (%)		9 (29.0%)	12 (40.0%)
Plantarflexed 1st ray n (%)		13 (41.9%)	15 (50.0%)
Prominent met heads n (%)		12 (38.7%)	8 (26.7%)
Loss of fatty pad n (%)		18 (58.1%)	13 (43.3%)
Oedema n (%)		4 (12.9%)	3 (10.0%)

(Table 5.5 Continued)		Active control insole group (n=31)	Optimised insole group (n=30)
Rombergs test	positive	1 (3.2%)	0 (0%)
	negative	30 (96.8%)	30 (100%)
Previous foot ulceration n (%)		16 (51.6%)	15 (50.0%)
Current foot ulceration n (%)		0 (0%)	0 (0%)

%'s are expressed as the proportion of group allocation, MTPJ – metatarsal phalangeal joint, cms-centimetres, STJ-subtalar joint, FPI-foot posture index, HAV-hallux abducto valgus, SD-standard deviation, IQR-Interquartile range

5.1.7 Blinding

The Bang Blinding Index (Bang, Ni & Davis, 2004) assessed participant blinding to the treatment allocation across both groups at the three, six, and 12 months follow-up period. The BI index ranged from -0.26 to 0.2 for the active control insole group and -0.476 to 0 for the optimised insole group indicating excellent blinding of participants to the intervention (Table 5.7).

Determination of FU by the examination of uploaded photographs taken of the participant's feet, a BI of 1.0 indicated that there was no occasion when the assessor could identify the treatment allocation of the participants.

Table 5.6 Bang's Blinding Index for participant blinding by treatment group allocation

Follow up time point	Active control insole group	Optimised insole group
Three-months	0.2	0
Six-months	-0.26	-0.48
12-Months	0.16	-0.30

*Bang Index=number (*n*) of correct answers/total* n − n *of incorrect answers/total* n*. 1 indicates complete lack of blinding, −1 indicates opposite answers regarding treatment type, and 0 indicates perfectly conducted blinding (Bang, Ni & Davis, 2004).*

5.2 Objective 2: Assess the appropriateness and performance of outcome measures

Objective two of the study (see Chapter 4, section 4.19.2) was to assess the appropriateness and performance of outcome measures.

5.2.1 Regions of Interest

The protocol directed that up to three regions of interest (ROI) for each participant could be selected for the podiatrists' analysis. There were seven sites on the foot comprising the region of interest one (ROI-1) at baseline, of which 98.3% (n=60/61) were situated in the forefoot (figure 5.4). There were seven sites on the foot comprising the region of interest two (ROI-2) at baseline. All 39 sites were located in the forefoot. Region of interest three (ROI-3) comprised of four sites, three of which were situated in the forefoot and one in the hindfoot. Visual examination revealed a comparative and similar site location distribution across both groups for each ROI.

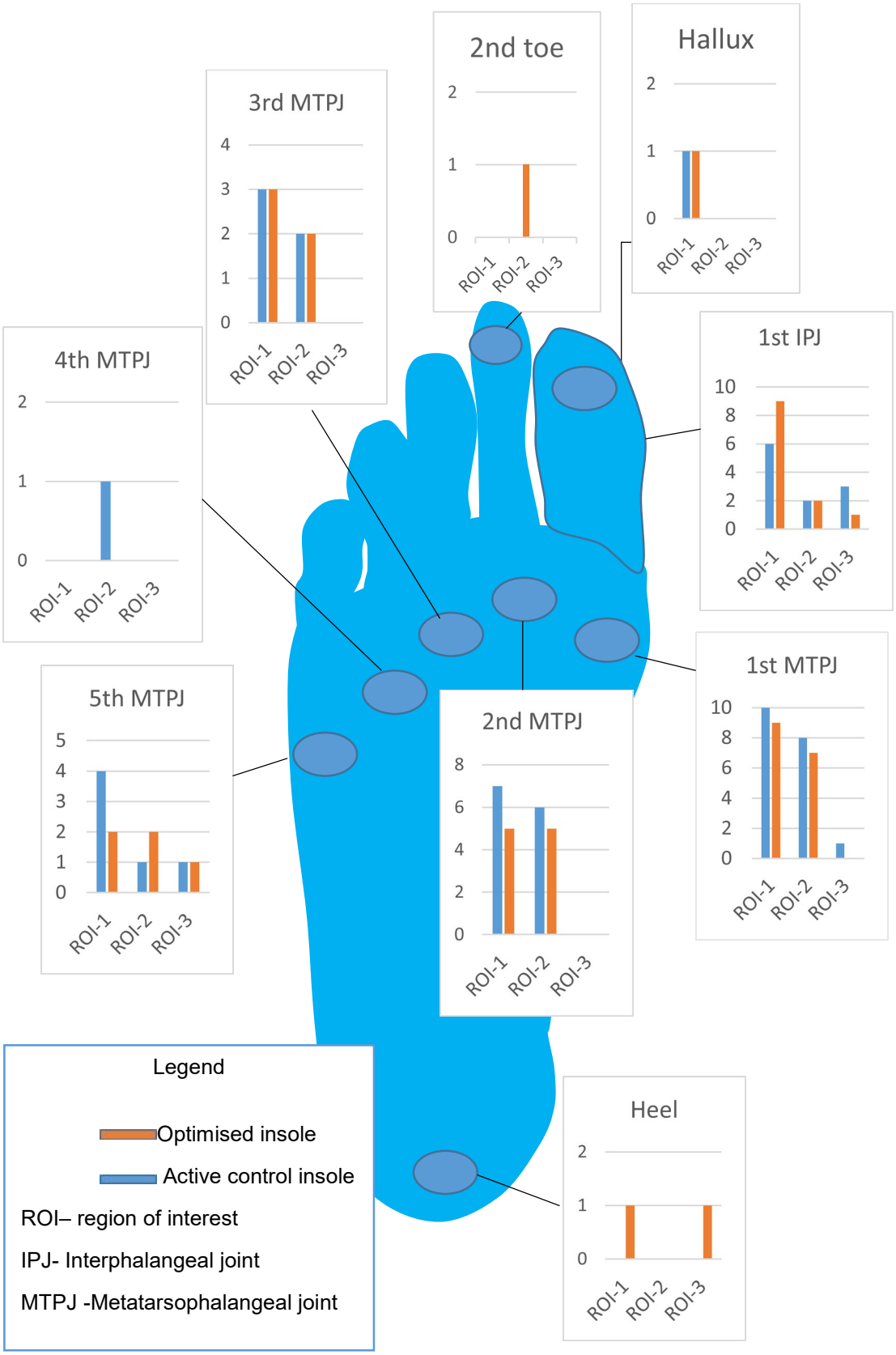


Figure 5.4 Comparison of region of interest sites by treatment group allocation

5.2.2 Gait patterns

Differentiation of gait patterns was undertaken at baseline by analysis of the Fscan data for all participants (Table 5.7). In total, there were 30 participants who identified with a propulsing gait pattern, 22 identified with a stomping pattern and nine with a variable gait pattern.

Table 5.7 Gait patterns by treatment group allocation

	Active control insole group (n=31)	**Optimised insole group (n=30)**
Propulsing gait (n)	13	17
Stomping gait (n)	13	9
Variable gait (n)	5	4

5.2.3 Insole modifications

Across the combined ROI's, 29 insoles did not require modification to achieve optimisation (Table 5.8). Sixteen insoles required one modification, and seven insoles required two modifications.

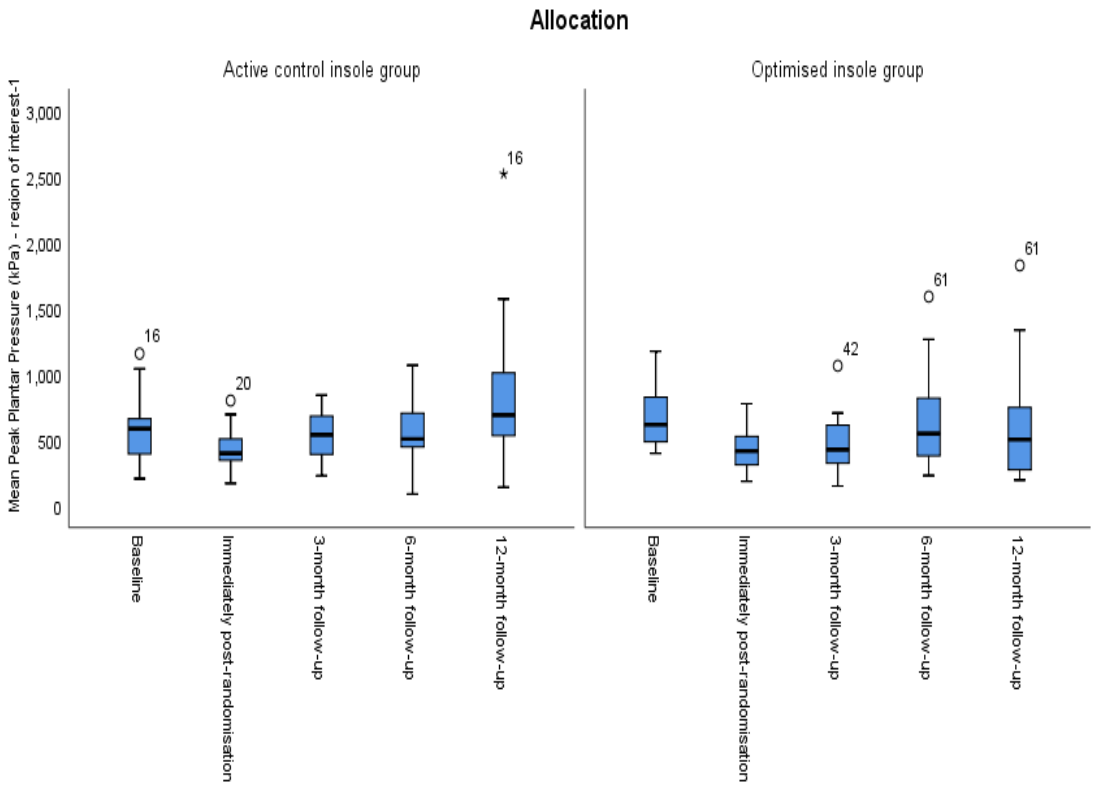
Table 5.8 Number of insole modifications for all regions of interest combined for the optimised insole group

	Propulsing gait (n=15)	**Stomping gait (n=30)**	**Variable Gait (n=7)**
Base insole (n,%)	11 (73.3%)	12 (40.0%)	6 (85.7%)
One modification (n,%)	3 (20.0%)	12 (40.0%)	1 (14.3%)
Two modifications (n,%)	1 (6.6%)	6 (20.0%)	0

% expressed as proportion of gait pattern

5.2.4 Plantar pressure - region of interest-1

Measurements of MPPP for the identified ROI's were taken at baseline, post-randomisation, and the three, six and 12-month follow-up sessions. Numbers of completed measures for ROI-1 ranged from 61 at baseline and post-randomisation, to 44 at three-months, 37 at six-months and 41 at 12-months follow-up (Table 5.9). At baseline, the mean of the MPPP for ROI-1 in Pulman-house shoes with no insole was 564.0 kPa (n=31) for the active control insole group and 583.3 kPa (n=30) for the optimised insole group. Immediately post-randomisation with the insoles' introduction, there was a reduction in MPPP for the active control insole and optimised insole groups compared to baseline (Table 5.9). At the three-month follow-up, the active control insole group increased in MPPP compared to baseline, with further increases in MPPP at six and 12-month follow-up. The optimised insole group reduced MPPP at three-months, but increased at six-months and 12-months compared to baseline. However, for both intervention groups the MPPP reduction was variable amongst participants. Comparisons of the absolute MPPP values at ROI-1 for the active control and optimised insole groups are visualised in figure 5.5 for each time point. Individual plots and trellis plots for ROI-1 can be viewed in Appendices four, five and six.



o= case number of outliers (greater than 1.5 to 3 times the Interquartile range), ★= outlier > 3 times interquartile range

Figure 5.5 Box plots of mean peak plantar pressure for region of interest-1 by treatment group allocation and follow-up time points.

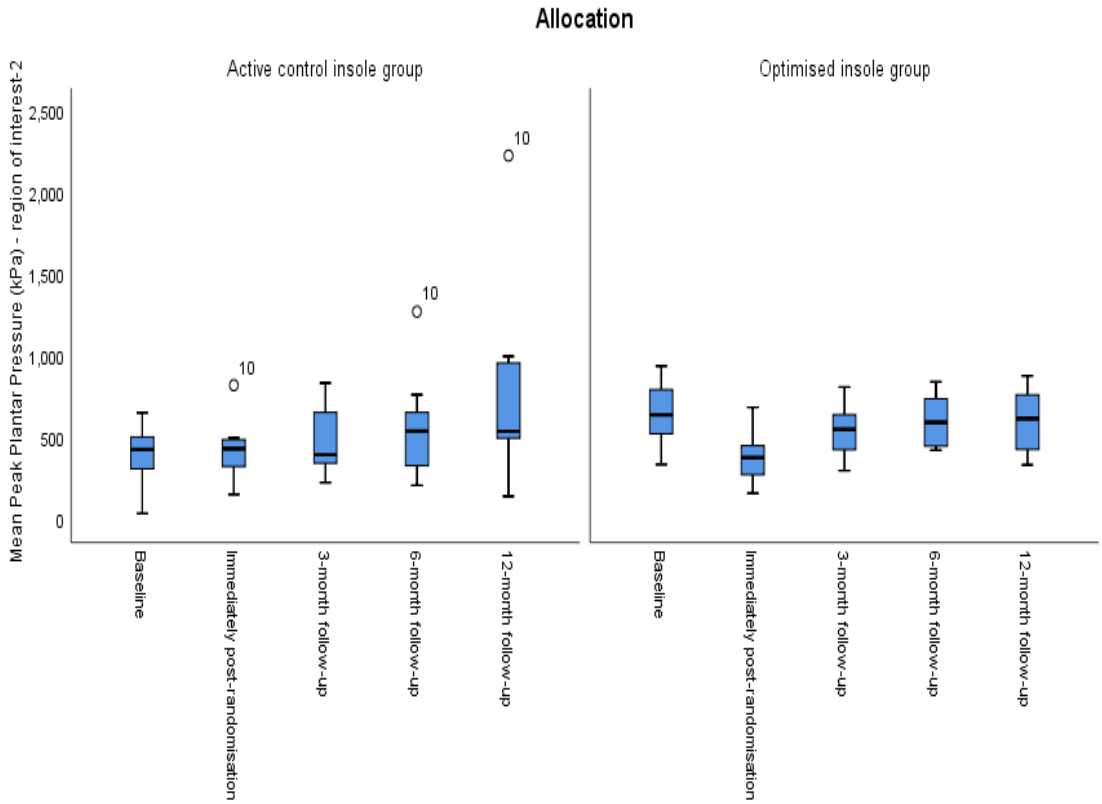
Table 5.9 Plantar pressure change for region of interest-1 by treatment group allocation and follow-up time points

	Active control insole Group (n=31)				Optimised insole group (n=30)			
	Number* (n)	**MPPP kPa (sd)**	**MPPP Difference** kPa (sd)**	**MPPP Difference** %**	**Number* (n)**	**MPPP kPa (sd)**	**MPPP Difference** kPa (sd)**	**MPPP Difference** %**
Baseline without insoles	31	564.0 (223.0)	n/a	n/a	30	583.3 (220.9)	n/a	n/a
Immediately post randomisation	31	447.4 (181.9)	-116.6 (126.0)	-20.1%	30	370.2 (162.1)	-215.2 (137.6)	-36.9%
3-month follow-up	20	546.1 (229.6)	+11.7 (194.1)	+2.1%	24	495.9 (244.4)	-112.0 (313.7)	-19.2%
6-month follow-up	19	639.8 (332.3)	+45.8 (251.5)	+8.1%	18	625.3 (353.8)	-5.6 (320.5)	-1.0%
12-month follow-up	19	854.7 (538.9)	+242.2 (445.3)	+42.9%	22	596.2 (437.6)	-17.8 (404.0)	-3.1%

**number of completed measures; ** difference calculated from baseline; MPPP-mean peak plantar pressure (kPa), n/a-not applicable, minus (-) indicates a reduction in MPPP, plus (+) indicates an increase in MPPP*

5.2.5 Plantar pressure - region of interest-2

Numbers of completed measures for ROI-2 ranged from 39 at baseline and post-randomisation, to 27 at 3-months, 2) at six-months and 24 at 12-months follow-up (Table 5.10). At baseline, the mean of the MPPP for ROI-2 in Pulman-house shoes with no insole was 499.4 kPa (n=20) in the active control group and 583.3 kPa (n=19) in the optimised insole group. Immediately post-randomisation with the insoles' introduction, there was a reduction in MPPP for the active control insole and optimised insole groups compared to baseline (Table 5.10). At all follow-up periods, the active control insole group experienced increases in MPPP compared to baseline. The optimised insole group reduced absolute MPPP at three-months and six-months and increased MPPP at 12-months compared to baseline, although the within-group MPPP percentage only increased at 12-months. Comparisons between groups for the MPPP absolute values at ROI-2 are visualised in figure 5.6 for each time point. Individual plots and trellis plots for ROI-2 can be viewed in Appendices seven, eight and nine.



o= case number of outliers (greater than 1.5 to 3 times the Interquartile range)

Figure 5.6 Box plots of mean peak plantar pressure change for region of interest-2 by treatment group allocation and follow-up time points

Table 5.10 Plantar pressure change for region of interest-2 by treatment group allocation and follow-up time points

	Active control insole Group (n=31)				Optimised insole group (n=30)			
	Number* (n)	**MPPP kPa (sd)**	**MPPP Mean difference** kPa (sd)**	**MPPP difference** %**	**Number* (n)**	**MPPP kPa (sd)**	**MPPP Mean difference** kPa (sd)**	**MPPP difference** %**
Baseline without insoles	20	499.4 (240.4)	n/a	n/a	19	583.3 (220.9)	n/a	n/a
Immediately post randomisation	20	452.7 (252.2)	-40.1 (211.8)	-7.4%	19	360.9 (157.3)	-208.3 (173.1)	-36.6%
3-month follow-up	12	648.6 (378.9)	+182.8 (288.2)	+33.9%	15	495.9 (244.4)	-87.1 (275.9)	-15.3%
6-month follow-up	11	717.0 (476.6)	+266.2 (446.1)	+49.3%	9	525.3 (253.8)	-31.7 (188.4)	-5.6%
12-month follow-up	11	797.1 (592.7)	+393.1 (639.7)	+72.9%	13	596.2 (437.6)	+62.6 (279.6)	+10.9%

**number of completed measures; ** difference calculated from baseline; MPPP-mean peak plantar pressure (kPa), n/a-not applicable, minus (-) indicates a reduction in MPPP, plus (+) indicates an increase in MPPP*

5.2.6 Plantar pressure - region of interest-3

Numbers of completed measures for ROI-3 ranged from eight at baseline and post-randomisation, four at 3-months, two at six-months and five at 12-months follow-up (Table 5.11). At baseline, the mean of the MPPP for ROI-3 in Pulman-house shoes with no insole was 425.8 kPa for the active control insole group and 474.7 kPa for the optimised insole group. Immediately post-randomisation with the insoles' introduction, there was a reduction in MPPP for the active control insole and optimised insole groups than baseline (Table 5.11). At the follow-up periods, although the active control insole group experienced increases in absolute MPPP compared to baseline, the within-group percentage change of MPPP increased. The optimised insole group reduced MPPP at three-months and increased MPPP at 12-months compared to baseline. There was no data for six-months. No box-plot was completed due to the low sample numbers. Individual plots and trellis plots for ROI-3 can be viewed in Appendices 10, 11 and 12.

Table 5.11 Plantar pressure change for region of interest-3 by treatment group allocation and follow-up time points

	Active control insole group				Optimised insole group			
	Number* (n)	**MPPP kPa (sd)**	**MPPP Mean difference** (sd)**	**MPPP difference** %**	**Number * (n)**	**MPPP kPa (sd)**	**MPPP Mean difference** (sd)**	**MPPP difference** %**
Baseline without insoles	5	425.8 (91.6)	n/a	n/a	3	474.7 (197.3)	n/a	n/a
Immediately post randomisation	5	298.6 (115.9)	-127.2 (88.1)	-29.9%	3	346.3 (138.0)	-128.3 (270.4)	-27.0%
3-month follow-up	2	377.5 (147.8)	+12.0 (42.4)	+2.8%	2	391.5 (306.2)	-125.0 (46.7)	-26.3%
6-month follow-up	2	337.5 (9.2)	-28.0 (96.2)	+6.6%	0	n/a	n/a	n/a
12-month follow-up	3	568.0 (245.2)	+155.3 (170.8)	+36.5%	2	685.5 (450.4)	+140.0 (668.9)	+29.5%

**number of completed measures; ** difference calculated from baseline; MPPP-mean peak plantar pressure (kPa), n/a-not applicable, negative indicates a reduction in MPPP, positive indicates an increase in MPPP*

5.2.7 Incidence of plantar foot ulceration

There were 17 incidences of foot ulceration during the 12 months of the study, occurring in 22.5% (n=7/31) of the active control group participants and 33.3% (n=10/30) of the optimised insole group. Foot ulceration was defined as a break in the skin epidermis, and all occurrences were determined by self-report of adverse events.

5.2.8 Safety – Adverse events

There were 26 AE's involving 17 participants for the duration of the study (Table 5.12). Of the AE's reported, 34.6% (n=9/26) were in the active control insole group, and 65.4% (n=17/26) were in the optimised insole group. Ten were considered attributable to the trial intervention and six not to be attributable to the intervention. Of the 17 incidences of ulceration, 16 were considered not attributable to the intervention.

Table 5.12 Adverse events by treatment group allocation

	Active control insole group	Optimised insole group	Total
Foot ulceration (probably attributable to intervention), n (%)	0 (0%)	1 (3.8%)	1 (3.8%)
Foot ulceration (not attributable to intervention), n (%)	7 (26.9%)	9 (34.6%)	16 (61.5%)
Falls (attributable to intervention), n (%)	0 (0%)	2 (7.7%)	2 (7.7%)
Foot rubs (attributable to intervention), n (%)	1 (3.8%)	0 (0%)	1 (3.8%)
Blisters (attributable to intervention), n (%)	0 (0%)	4 (15.4%)	4 (15.4%)
General musculoskeletal & postural pain (attributable to intervention), n (%)	1 (3.8%)	1 (3.8%)	2 (7.7%)
Total n, (%)	9 (34.6%)	17 (65.4%)	26 (100%)

% is expressed as a proportion of total Adverse Events

5.2.9 Safety - Serious Adverse Events

There were six SAE's involving three participants. All were unrelated to the trial intervention. One participant had four SAE's categorised as sequelae associated with bladder cancer. This involved life-threatening episodes, hospitalisation and serious medical episodes (n=3), and eventual death (n=1). One participant had a lower leg amputation due to a malignant melanoma categorised as hospitalisation and serious medical episode. One participant was hospitalised after trauma to the foot.

5.2.10 Completed questionnaires and items reporting self-footcare

The Nottingham Assessment of Functional Footcare questionnaire (Lincoln *et al.*, 2007) was used to assess the participants' engagement with their foot care. The proportion of questionnaires returned at baseline was 98.3% (60/61). Returns were consistent across the follow-up time points (3-month, 72.1% (n=44/61), 6-month, 62.3% (n=38/61), 12-month, 68.9% (n=42/61). There was a similar distribution of returns from both intervention groups. The proportion of footcare questionnaires returned across the study duration by intervention group ranged from 61.3% (n=19/31) to 100% (n=31/31) by the active control insole group and 73.3% (n=22/30) to 96.7% (n=29/30) for the optimised insole group.

Participant completion rates of the footcare questionnaire, answering more than 80% of questions in the returned questionnaires, ranged from 95% to 98% across the study time points. No differences were noted between the active control insole and optimised insole groups. Out of the 26 items, five questions produced the most missing data at baseline. These related to wearing slippers with no fastening (n=3), wearing shoes without socks (n=3), wearing artificial fibre socks (n=3), applying a dry dressing to a blister (n=3), and putting a dry dressing on a graze (n=3).

5.2.11 Completed questionnaires and items reporting physical activity levels

The International Physical Activity Questionnaire (Booth, 2000) was used for participants to self-evaluate their activity levels. There were high participant

completion rates of the activity questionnaire. All participants returning questionnaires at each time point completed more than 80% of the questions.

The proportion of questionnaires returned at baseline was 98.3% (60/61). Returns were consistent across the follow-up time points (3-month, 72.1% (n=44/61), 6-month, 62.3% (n=38/61), 12-month, 68.9% (n=42/61). The proportion of activity questionnaires returned across the study duration by treatment allocation ranged from 58.1% (n=18/31) to 100% (n=31/31) by the active control insole group and 73.3% (n=22/30) to 96.7% (n=29/30) for the optimised insole group.

5.2.12 Proportion of participants adhering to wearing the insoles

Forty-four participant uploads were completed for the data logger to assess adherence to the wearing of the insoles. The total wear time determined by the data logger ranged from 259 hours to 12552 hours for the active control insole group and 261 to 13176 hours for the optimised insole group. The mean wear time ranged from 45.5% (n=20) of participants wearing the insole for less than four hours per day, 38.6% (n=17) for four to eight hours per day, and 15.9% (n=7) for more than eight hours a day (table 5.13). There was little variation for wear time across treatment groups.

Table 5.13 Adherence to wearing the insole by treatment group allocation

Time wearing insole/day	Active control insole group (n=19)	Optimised insole group (n=25)	Total (n=44)
<4 hours	9 (47.3%)	11 (44.0%)	20 (45.5%)
4-8 hours	7 (36.8%)	10 (40.0%)	17 (38.6%)
>8 hours	3 (15.8%)	4(16.0%)	7 (15.9%)

%'s expressed as a proportion of treatment group allocation

5.2.13 Plantar pressures – a signal of efficacy

As an indication of a signal of efficacy, the between-group differences of the change in MPPP from baseline to each follow-up time-point were calculated for ROI-1, ROI-2, and the mean of all ROI's (Table 5.14). ROI-3 was not calculated due to the low numbers within this sub-sample. Assessing ROI-1, ROI-2 and ROI-combined ensures that any effect from the intervention on the other regions-of-interest were also evaluated. Both the unadjusted and adjusted for baseline plantar pressure (to account for possible regression to the mean) data are presented using analysis of covariance.

Whilst this study was not powered to detect a statistical effect, the unadjusted and adjusted MPPP between-group difference for ROI-1, ROI-2 and all ROI's combined suggests a favourable reduction in MPPP with the optimised insole at all times periods, although the size of the MPPP difference varied across follow-up periods. Additionally, the within group differences (Tables 5.9, 5.10, 5.11) demonstrate MPPP reductions commensurate with the thresholds from the

IWGDF, which suggests that for those with DM and a recently healed diabetic foot ulcer, a threshold of 200kPa or a reduction of 30% or greater in absolute peak pressure during walking should be used (Bus *et al.*, 2020). Accordingly, at the appropriate level of confidence, it is plausible that similar differences in MPPP will be observed in the main trial (Sim, 2019).

Table 5.14 Change from baseline in plantar pressures by treatment group allocation for region of interest-1, 2 and all regions combined at each time point

	Region of interest -1		Region of interest-2		All regions of interest combined	
Time Point	**Mean MPPP difference unadjusted for baseline kPa(CI*)**	**Mean MPPP difference adjusted for baseline kPa(CI*)**	**Mean MPPP difference unadjusted for baseline kPA (CI*)**	**Mean MPPP difference adjusted for baseline kPA (CI*)**	**Mean MPPP difference unadjusted for baseline kPA (CI*)**	**Mean MPPP difference adjusted for baseline kPA (CI*)**
Immediately post randomisation	96.3 (CI 29.4,163.3)	89.2 (CI -36.7,141.7)	161.5 (CI 37.1,285.9)	136.7 (CI 26.8,246.6)	100.5 (CI 36.6,164.4)	87.9 (CI 40.1,135.7)
3-month follow-up	123.7 (CI -286.4,39.0)	77.3 (CI -61.5,216.2)	203.1 (CI-13.6,419.9)	187.3 (CI -28.8,403.5)	155.4 (CI 11.4,299.5)	122.2 (CI -5.0,249.5)
6-month follow-up	51.4 (CI -140.3,243.1)	44.5 (CI -148.5,237.5)	247.7 (CI 3.5,491.8)	283.9 (CI 36.0,531.8)	124.2 (CI -53.0,301.3)	112.0 (CI -63.4,287.4)
12-month follow-up	238.9 (CI -32.1,509.9)	239.4 (CI -35.4,514.2)	252.4 (CI -61.0,565.8)	283.6 (CI -55.9, 623.1)	257.9 (CI 15.9,500.0)	255.5 (CI 10.1,501.0)

**Confidence intervals expressed at 95%, kPa-kilopascals, MPPP – mean peak plantar pressure difference calculated from baseline*

5.2.14 Sample size estimate for the main trial

Foot ulceration is an important outcome to patients, and it is acknowledged that there remains some uncertainty around a minimally clinically important difference in MPPP. If the primary outcome of a future trial is a continuous variable such as MPPP, the primary analysis will be based on ANCOVA. This increases the precision of the treatment estimate compared to a simple t-test. Estimates of the standard deviation and (Table 5.15) and correlation coefficients for ROI-1 compared to baseline (Table 5.16) were calculated and can be visualised in Appendix 13.

Table 5.15 Estimates of the standard deviation (SD) of Mean Peak Plantar Pressure at each time-point (based on ROI-1)

	Combined			Active control insole			Optimised Insole		
	N	SD	80% CI	n	SD	80% CI	n	SD	80% CI
Baseline	61	220.3	197.8, 250.4	31	223.0	192.5, 269.1	30	220.9	190.3, 267.6
Post-randomisation	61	176.7	158.7, 200.8	31	182.0	157.1, 219.6	30	164.4	141.6, 199.1
Month 3	44	236.4	208.6, 275.6	20	229.6	191.9, 293.2	24	244.4	207.2, 304.2
Month 6	37	338.2	295.3, 400.7	19	332.3	276.5, 427.7	18	353.8	293.1, 459.3
Month 12	41	498.2	437.8, 584.6	19	538.9	448.5, 693.6	22	437.6	368.5, 551.1

Sd- standard deviation, CI-Confidence interval

Table 5.16 Estimates of the correlation coefficient of baseline Mean Peak Plantar Pressure with follow-up MPPP at each time-point (based on ROI-1)

	Combined		**Active control insole**		**Optimised Insole**	
	n	r	n	r	n	r
Post randomisation	61	0.77 (CI 0.69, 0.83)	31	0.83 (CI 0.74, 0.89)	30	0.78 (CI 0.66, 0.86)
Month 3	44	0.34 (CI 0.15, 0.50)	20	0.67 (CI 0.46, 0.81)	24	0.10 (CI -0.18, 0.36)
Month 6	37	0.56 (CI 0.39, 0.69)	19	0.66 (CI 0.44, 0.81)	18	0.45 (CI 0.15, 0.67)
Month 12	41	0.48 (CI 0.31, 0.62)	19	0.58 (CI 0.33, 0.75)	22	0.39 (CI 0.12, 0.61)

n –number of completed measures, r – correlation coefficient, CI-80% Confidence intervals

Based on estimates from the feasibility data (Table 5.15 and Table 5.16), a series of scenarios were considered for potential sample size estimates should the primary outcome be MPPP. Calculations are based on a significance level of $\alpha = 0.05$ (two-sided) and 90% power (Table 5.17). The base case sample size calculation conservatively uses information on the upper 80% confidence limit of standard deviation of MPPP at six-month follow—up (i.e. 400kPa) and standardized effect size of 0.4, considered to be small-to-moderate. An additional inflation of 30% to account for a drop-out rate was added to each estimate.

To calculate the target sample size, the primary outcome variable for the full-scale trial will be MPPP at six-months based on in-shoe pressure measurement. The six-month time-point was selected as this is when the optimised insole no

longer reduces MPPP compared to baseline at ROI-1 and ROI-2. In the absence of clinical information regarding what constitutes a clinically important difference in MPPP reduction, we assumed that a difference of 160kPa (30% reduction from baseline of all ROI's) is important, translating to a standardised effect size of 0.4, usually considered small-to-moderate. As the planned analyses would include an adjustment for baseline MPPP, the effect of allowing for the correlation between baseline and six-month MPPP has also been considered. Using the correlation coefficient of 0.55 to improve the precision of the estimate and an allowance of 30% for drop-out, it is estimated that the multi-centre trial would require 265 participants in total to provide 90% power at the 5% (two-sided) significance level. This would give a definitive indication of clinical effectiveness and allow a small-to-moderate effect size to be detected.

Table 5.17 Sample size scenarios

	MPPP diff (MCID)	SD	Effect Size	Correlation	LTFU	Unadjusted	Adjusted for LTFU
Base Case	**160**	**400**	**0.40**	**0**	**30%**	**265**	**379**
Vary MCID	180	400	0.45	0		210	300
	200	400	0.50	0		171	245
	220	400	0.55	0		141	202
Vary SD	160	420	0.38	0		293	419
	160	460	0.35	0		346	495
	160	500	0.32	0		413	590
Vary correlation	160	400	0.40	0.15	30%	260	372
				0.25		249	356
				0.35		233	333
				0.45		212	303
				0.55		185	265
				0.65		154	220

MPPP-mean peak plantar pressure, MCID-minimally clinical important difference, SD-standard deviation, LTFU-loss to follow-up

5.3 Chapter summary

This chapter has presented the results from the quantitative aspect of the INSTEP fRCT. These results addressed the first and second objectives of the study; to assess the feasibility and acceptability of the trial procedures, and to assess the appropriateness and performance of outcome measures. The next chapter will present the findings from the embedded qualitative study in order to address the third objective of the feasibility study; to explore the experiences of participants' receiving optimised insoles and house-shoe, or the active control

insole and house shoe, and podiatrist's experiences of delivering the intervention.

Chapter 6 Qualitative findings of embedded qualitative study

This chapter presents findings of the embedded qualitative study of the INSTEP fRCT. Accordingly, this chapter complements chapter five, which described the quantitative results. The discussion of the results related to the study objectives is discussed in chapter seven.

6.1 Objective 3: To explore the experiences of participants' receiving and podiatrist's experiences of delivering the intervention

The findings relate to the third research objective: To explore the experiences of participants' receiving optimised insoles and house-shoe, or the active control insole and house shoe, and podiatrist's experiences of delivering the intervention. This information will inform the refinement and development of the anticipated definitive RCT.

6.2 Data collection

Fifteen face-to-face semi-structured interviews were conducted, involving twelve participants with diabetes who had participated in the feasibility RCT and three podiatrists who had delivered the study intervention. Six study patient participants with diabetes (hereon called patient participants) had been allocated to the optimised insole group and six allocated to the active control insole group with equal numbers purposively sampled from each study site. Of the three podiatrists, one was from each study site.

All interviews were conducted in the participant's preferred location. Six patient participants chose to be interviewed in their homes and six chose the podiatry

treatment room. The three podiatrists were interviewed at their respective clinical locations.

6.3 Participant characteristics

Patient participants and podiatrists' names have been replaced with an identifier number to ensure anonymity is maintained. A detailed description of each podiatrist is not provided as those familiar with the study and sites might identify each podiatrist by this description.

Eleven of the patient participants were male and one was female (Table 6.1). Recruitment to increase the proportion of female participants to reduce sample bias was attempted but was not achieved. This was due to female participants dropping out (n=3), lack of time (n=2), and not wanting to be interviewed (n=2). Two of the podiatrists were male and one was female. Patient participants' mean age was 71 years with a mean duration of diabetes of 18 years, compared to a mean age of 69 years and a mean duration of diabetes of 21 years for the whole feasibility study population. Podiatrists' age ranged from 36 to 58 years and the length of time practising as a podiatrist ranged from six to 27 years. The podiatrists were all musculoskeletal specialists.

Table 6.1 Patient participant's characteristics

Participant	Gender	Age (years)	Duration of diabetes (years)	Treatment arm
0105	Female	84	12	Active control insole
0110	Male	64	17	Optimised insole
0117	Male	68	25	Optimised insole
0116	Male	64	22	Active control insole
0202	Male	70	23	Optimised insole
0203	Male	72	24	Active control insole
0205	Male	70	4	Active control insole
0208	Male	72	14	Optimised insole
0307	Male	65	15	Active control insole
0315	Male	71	15	Active control insole
0316	Male	83	18	Optimised insole
0318	Male	73	30	Optimised insole

6.4 Findings

Thematic analysis revealed three themes:

1. Accepting the study,
2. Behaviour and support during study procedures,
3. Impact from study participation.

These three themes were built upon different sub-themes occurring from patient participants and podiatrists (Figure 6.1). The findings are presented per theme

with the sub-themes of both patient participants and podiatrists. A summary of the narratives of the patient participants (Table 6.2) and podiatrists (Table 6.3) are presented.

Figure 6.1 Themes and subthemes of patient participants with diabetes and podiatrists

Table 6.2 Identified narratives of themes and sub-themes from patient participants

Theme	Subtheme	Patient participant narratives
Accepting the study methods	Participant recruitment	"Well, because I was asked. It was someone from the clinic. They check my feet and asked me if I wanted to take part. So I did." (0203)
	Participant Information	"Well, I understood all the information sheets. Yes and all it entailed, yes I found it quite clear and precise and there was no unexpected things as the trial went on, I didn't say, oh I never knew that there was nothing of that." (0103) "Too long ago to remember! (Laughed loudly!) I remember it was long and very detailed." (0315)
	Randomisation	"I said well, no I don't mind and, in a way, the whole point of the trial, as far as I am concerned is that I didn't know!" (0202) "But no, I don't really have in that sense I realise that I could be, it's randomly selected and I could be in either of the two groups and I'm happy to participate regardless of which group I am in. Ultimately if it helps the research to draw some conclusions, that's the main purpose" (0318)
	Questionnaires	'That you would want so you would say well, I guess I'm in the nearest one to that, you know, do you do it frequently; infrequently; rarely and that kind of thing and I think oh, I'm not sure which box to tick here. I feel I fall often somewhere between one or two of the boxes and so yes, that's true of many questionnaires.' (0318) "It was alright. I am not a great one for filling in paperwork but no problem really." (0202)
	Receiving the intervention	"Well, no effort from my point of view except I couldn't stand up. Because when you are doing the balance, because I can't balance very well, I was going over. So he ended up doing it 2/3 times." (0116)
Behaviour and support during study procedures	Foot-care	"Didn't realise how important it was to really look after the feet." (0110)
	Participation rationale	"It may be a bit late in life for it to affect me, but the generations that come along afterwards, surely they deserve the better treatment if it transpires that there is a better treatment, so that's why, purely and simply for future generations!" (0208)

Table 6.2 (continued) Identified narratives of themes and sub-themes from patient participants

Behaviour and support during study procedures	Family	"My wife has to tell me to take them off when I go out because I forget. She says 'go change your shoes'." (0114)
	Study support	"When I got there, they made me very welcome. They explained to me what they were going to do and didn't rush anything and it was very good. She sat me on that couch and explained everything to me about what they were going to do; what they did." (0205)
	House shoes	"Tend to use them mostly when I'm in the house for any length of time or sort of, when you first get up in the morning and things like that." (0318)
Impact of study involvement	Location & logistics	Gives me a day out, really, a ride on the bus and the boat but that's the only thing! (0208)
	Diabetes impact	"It's just that I've got to be careful about what you eat and what not." (0202)
	Overall Experience	To be negative about it, I would say there are no negatives as far as I am concerned, that might sound you know good or bad I don't know. From my perspective, it's worked 100%." (0307) "Perhaps one day you won't have to use all those wires and that. Do you know what I mean? Perhaps the old computer could do exactly the same job, do you know what I mean because it looked a bit old fashioned. Connecting you up to all those cables like they got now, but it done the job, really good!" (0205) "I enjoyed it, yes I did enjoy it…… I just say that I found it interesting" (0103)
	Receiving the study results	"Well, purely out of interest because you've been involved in something, it would just be interesting to know a) If I've got the real one or not and b) Whether the trial proved that there is an area there that can be improved if we do whatever, or there is scope for improvement." (0208)

Table 6.3 Identified narratives of themes and sub-themes from podiatrists

Theme	Subtheme	Podiatrist narratives
Accepting the study methods	Recruitment to study	"I think we did ok, but I'm still disappointed we didn't reach our target because I thought that would be easily achievable within the time and I can't think as to why we didn't meet that target; I still don't know. Were people asking? I'm sure they were because I was involved I definitely annoyed them with my emails every week so!" (03P)
	Intervention delivery	"Quick and easy! Yeah, em, I think that sums it up, really. Em, there's no real theory to how we make them. You go to the algorithm of what type of insole you're going to put in for that particular patient. But what I come back to is it's fast, it's quick and that what we want!" (01P) "I did find it quite time-consuming and there was a lot of information on the first one! The second wasn't so bad but on the first initial assessment, I found it was quite a lot." (02P)
	Technology	"I mean, for a long time, it didn't work because we had IT issues. Yes, the equipment, sometimes I had a few issues with the Fscan, and then, of course, we couldn't download… we couldn't get the sensor reader to work with the computer, there was all that issue." (02P)
Behaviour and support during study procedures	Podiatrist networks	"Good to highlight the team. I knew a few of them, but it was good as you can get contact numbers so that you could discuss things between each other it's a good way of networking in the research team." (01P)
	Training	"Yes, the training session was good really enjoyed it, and well delivered and I think probably there were lots of questions I didn't ask that maybe I should have. Um, I think what might have been helpful for me was to do a scenario there after the training had been delivered." (03P)
	Participant interaction	"From a patient point of view, it's good for us to use it as a tool to show them what we are doing and make it more understandable. I found all the participants to be willing and able, all very pleased and happy to take part." (01P)

Table 6.3 (continued) Identified narratives of themes and sub-themes from podiatrists

Impact of study involvement	Overall participation	"…and just being part of the research process as well being able to see things from your perspective as well and understanding about how to pitfalls about setting up a project and I've done research myself but not on this sort of large scale, so that's been really interesting as well." (02P)
	Change in practice	"Yeah, it's made me stop and think about what we do, you know you've just got you, you do things out of habit a lot of the time because that's how you've always done them. And then you use the F Scan and you suddenly think oh, actually, that's not doing what you expected it to do." (02P)
	Dissemination	"I would like to discuss the findings with the team. I don't know if you'd be happy coming down and presenting your findings to the team but I think that would be amazing to show clinicians who have been involved in it." (03P)

6.4.1 Accepting the study methods

The first theme is named ‘accepting the study methods’ and describes the appropriateness and suitability of the study methods procedures as experienced by the patient participants and podiatrists. Patient participants and podiatrists revealed their views and experiences of the study practices and the processes associated with delivering and receiving the insole and house-shoe. Five sub-themes emerged from the interviews with the patient participants; participant recruitment, participant information, randomisation, questionnaires, and receiving the intervention (Table 6.2). Three sub-themes emerged from the interviews with podiatrists; recruitment to study, intervention delivery, and the technology involved in the study (Table 6.3).

6.4.1.1 Patient participant recruitment

All patient participants spoke of the influence of clinical staff to their recruitment to the study. Being approached by a podiatry team member during their regular NHS appointment and asked to take part was paramount to their decision to participate, as two participants advocated:

> “Well, because I was asked. It was someone from the clinic. They check my feet and asked me if I wanted to take part. So I did.” (0203)

> “The podiatrist asked me to (take part), someone who works there. He asked me whether I would and I said, fair enough!” (0202)

The propensity of the clinical staff to make patients aware of the study and the prominence of this within the conversation was the principal explanation provided for patient participants to be recruited.

6.4.1.2 Patient participant information

Most of the patient participants reported that the study information received before consenting to participate in the study was clear and understandable. This information enabled them to make informed decisions to become involved. The patient information sheet, in particular, was highlighted by patient participants:

> "Well, I understood all the information sheets. Yes and all it entailed, yes I found it quite clear and precise and there was no unexpected things as the trial went on, I didn't say, oh I never knew that, there was nothing of that." (0103)

Acknowledgment of the contents and structure of the patient information sheet assured the ability to communicate study details to participants. However, two patient participants commented that the patient information sheet was too long and the recall of specific contents was lost over time, as one participant highlighted:

> "Too long ago to remember! (Laughed loudly) I remember it was long and very detailed." (0315)

6.4.1.3 Randomisation

All patient participants commented that the randomisation process was acceptable and did not prevent them from consenting to participation. Most participants highlighted awareness of randomisation and acknowledged that it was an accepted part of a clinical trial, as some patient participants mentioned:

> “I said well, no I don’t mind and, in a way, the whole point of the trial, as far as I am concerned is that I didn’t know!” (0202)

> “But no, I don’t really have in that sense I realise that I could be, it’s randomly selected and I could be in either of the two groups and I’m happy to participate regardless of which group I am in. Ultimately if it helps the research to draw some conclusions, that’s the main purpose.” (0318)

The level of understanding of randomisation may have assisted in some participants accepting the process as part of the study procedure. For those patient participants without a knowledge of the process, they voiced uncertainty as to what randomisation involved:

> “Because I didn’t understand the difference, but it didn’t bother me. I didn’t question the fact of why, what’s the difference, well you know this is how you do a trial. If you’re trialling pills, you give some people placebo things and the others the right stuff and don’t tell them so that’s the way I looked at it, rightly or wrongly but that’s how I found it to be; that’s how it worked with me anyway” (0103).

This patient participant reported that while they did not necessarily comprehend the true meaning and consequences of randomisation, it did not affect their decision to participate in the study.

6.4.1.4 Questionnaires

Many patient participants reported various difficulties in completing the Patient-Reported Outcome Measure (PROM) questionnaires by finding some of the classifications challenging to answer precisely. Patient participants specifically found the categories assessing their activity levels too indiscreet and hard to relate to their circumstances:

> "I guess I'm in the nearest one to that, you know, do you do it frequently; infrequently; rarely and that kind of thing, and I think oh, I'm not sure which box to tick here. I feel I fall often somewhere between one or two of the boxes and so yes, that's true of many questionnaires." (0318)

> "It's an interesting point in that the questions were all geared in the first questionnaire I did, about a month ago now, were all geared to a fit person. Whereas I've had a stroke and a fractured leg, and as I say, I was bedbound for eight months with this (points to left ankle). And when it says things like how much exercise you get, getting out of bed in the morning is a major bit of exercise. I still can't undo my trousers and do them up. You know, but it's all effort so I had to count that in what you wanted with the question. But it might not necessarily be what you want, because you are after 'em, something like a brisk walk, thing like that. Any walk on my walker is a brisk walk to me." (0116)

Despite difficulties with the content of the questionnaires, the patient participants highlighted that the PROMs were acceptable in terms of the time taken to complete and appropriateness of format and layout. Two participants reported:

"It was alright. I am not a great one for filling in paperwork but no problem really." (0202)

"The way that you laid them out, they were laid out was brilliant! They were very good." (0205)

6.4.1.5 Receiving the intervention

The process for collecting the in-shoe pressure measurements and receiving the house-shoe and insole produced various observations from the patient participants. Some patient participants spoke of how they had struggled with the walking and balance task as part of the Fscan sensor calibration:

"Well, no effort from my point of view except I couldn't stand up. Because when you are doing the balance, because I can't balance very well, I was going over. So he ended up doing it 2/3 times……But it was like walking across the room; I got caught because I was suddenly going too fast. I think, from my point of view, I wanted to get to that wall. Because it was safety." (0116)

"Trying to keep my balance and I was a bit worried about that." (0114)

Undertaking a new physical task can be accompanied by uncertainty when a prior disability is in situ. Other observations were emotional responses that were conveyed by some patient participants concerning the process for collecting the in-shoe pressure measurements:

"It felt strange, I was a tiny bit apprehensive when I went there they put the shoes on, and they connected me up with all the pads and that and I walked along the line." (0205)

> “But it wasn’t always bad or uncomfortable; it was just that I had to walk up and down and was pulling these cables behind me.”(0202)

Many of the patient participants indicated that the impact of the time commitment (1.5 hours) to undertake the study procedures was long, but not burdensome. Some stated that they were able to consign the time to the study as they were retired, as two participants highlighted:

> “Luckily for me, it’s easy being retired, so time is not a problem. But it could be for some other people.” (0114)

> “I don’t mind doing it, but it's time-consuming. Well, that personally, was ok. I’ve got nothing else to do, it’s only me and the wife and just went and done it.” (0203)

Other patient participants reported other outside interests which could influence their continued involvement in the study, as two participants suggested:

> “I mean as long as I am given enough time because I do a bit of driving for Hospice care and things like that. It’s no problem!” (0315)

> “We’ve got a family living in France, and we spend quite a bit of time out there. We kind of roughly split our year, slightly less than half but more or less half and half between the UK and France.” (0318)

6.4.1.6 Recruitment to the study

The three podiatrists consistently reflected on their struggles to recruit participants to reach their site target. They spoke of their efforts to engage other

team members to screen patients to recruit for the study and the personal burden this created. Two podiatrists revealed their attempts by highlighting:

> “I think we did ok, but I’m still disappointed we didn’t reach our target because I thought that would be easily achievable within the time and I can’t think as to why we didn’t meet that target; I still don’t know. Were people asking? I’m sure they were because I was involved I definitely annoyed them with my emails every week so. Yes, I bombarded them with emails or I sort of carpet
>
> bombed them with emails every week. We have talked about it at staff meetings, as well as you’ve come up initially and explained it to them and they were happy with that. So initially I started just in clinic recruiting and then I found there wasn’t really enough people that were being recruited so we put it out to different places and then those people had to be, I suppose, reminded of the criteria.” (03P)

> “It’s a shame we couldn’t recruit more people….we tried, but just couldn’t find them. I tried to get others (podiatrists) to get people, but it seemed that although they were up for it, most never sent any in.” (02P)

Utilising different strategies to engage colleagues to identify and screen patients was not successful and left the podiatrists feeling dejected for the failure of the study site to recruit to its target.

6.4.1.7 Intervention delivery

The delivery and manufacture of the house shoes and insoles by the three

podiatrists were acceptable in following the algorithm process. All three podiatrists clarified that the insole algorithm for designing the insole was straightforward to follow, as one suggested:

> “Quick and easy! Yeah, em, I think that sums it up, really. Em, there’s no real theory to how we make them. You go to the algorithm of what type of insole you’re going to put in for that particular patient. But what I come back to is it’s fast, it’s quick and that’s what we want.” (01P)

However, some elements were problematic to the podiatrists, especially the time to provide the intervention. The time to fabricate and deliver the intervention at the first study appointment was problematic for all podiatrists, as one highlighted:

> “I did find it quite time-consuming and there was a lot of information on the first one. The second wasn’t so bad but on the first initial assessment, I found it was quite a lot.” (02P)

In addition to the time element, one of the podiatrists highlighted fitting issues when delivering the house-shoe and insoles, as one put forward:

> “Some of the shoes were a bit difficult to fit with the optimised insole, sometimes it was difficult to stop the heel slipping, and I always, sort of, adjusted the heel bit because you’ve got that separate heel adjustment.” (01P)

6.4.1.8 Technology

The increased use of technology as part of the delivery of the intervention within the clinical environment was positively embraced by the podiatrists and proved acceptable to them all:

> “And that’s just what it does! It’s easy, you know, it’s simple there’s no em complications to it, em nothing I thought oh, oh is it going to work! Because the measurements tell you it does.” (01P)

One consistent concern that the podiatrists highlighted was the complications arising from the technical support systems. The challenges of setting up the Fscan and data logger systems because of the restrictions imposed by NHS Information Technology (IT) governance was highlighted by all of the podiatrists:

> “The main other issue as we’ve discussed in the past is the system on an NHS computer. We’ve had to go through a lot of hoops with information governance to be able to install it on our computers, which has taken up a lot of additional time. Not just from myself but from the information governance team, they’ve been. It’s been on two meeting agendas, and it has passed obviously but we had to get some information about coding from the American software supplier which was crazy but yeah, it all worked out in the end.“ (03P)

> “I mean, for a long time, it didn’t work because we had IT issues. Yes, the equipment, sometimes I had a few issues with the Fscan, and then,

of course, we couldn't download… we couldn't get the sensor reader to work with the computer, there was all that issue." (02P)

The frustration of delays in receiving NHS IT support when setting up the Fscan equipment and data logger software was considerable. One of the podiatrists suggested that a future study may consider this aspect and proposed a solution to overcome this hurdle:

> "If the project could have its own IT support, it would be a lot easier but then I know that that creates problems because each Trust wants to be responsible for its own IT, but if you could actually have IT support just for the study so that you could by-pass having to use the Trust's IT, I think that would definitely help." (02P)

6.4.2 Behaviour and support during study procedures

The second theme is named 'behaviour and support during study procedures' and describes the behaviour and support experienced by those interviewed. This theme relates to factors that influenced their conduct and actions during their study involvement. Five sub-themes emerged from the interviews with the patient participants; foot-care, participation rationale, family, house-shoes and study support (Table 6.2). Three sub-themes emerged from the interviews with podiatrists; podiatrist networks, training and participant interaction (Table 6.3).

6.4.2.1 Foot-care

All patient participants spoke with a varying degree of awareness about undertaking foot-care activities during the study which could impact their risk of

developing foot complications. Two of the participants recognised the importance of foot-care activities in reduce the risk of DFU by highlighting:

> “I didn’t realise how important it was to really look after the feet.” (0110).

> “But no, I do try and I do know it’s only down to me, it’s my body.” (0103)

Other participants relied more on health services to assist with their foot-care provision, although this requirement prompted awareness of preventing potential foot complications, as one patient participant highlighted:

> “The fact that I go every six weeks to have my feet checked and done, my toenails cut and everything like that it just prevents; obviously, it turning into an ulcer and really that’s the thing.” (0307)

The variability of patient participants’ awareness of foot-care is apparent. It appears to influence their ability to perform tasks or rely on other providers to help with the activities.

6.4.2.2 Participation rationale

Patient participants reported different reasons for choosing to participate in the study. Some described behavioural values associated with altruism, as one participant highlighted:

> “It may be a bit late in life for it to affect me, but the generations that come along afterwards, surely they deserve the better treatment if it transpires that there is a better treatment, so that’s why, purely and simply for future generations!” (0208)

Other patient participants conveyed different motives for taking part in the study. These related to expectations of improvements in their foot care, as one participant suggested:

> “prevention is better than cure etc. that I just thought it would be a good opportunity, if it helps me which, since that time since you got them new insoles in my feet, I haven’t had any problems.”(0315)

6.4.2.3 Family

Many patient participants highlighted the importance of the supportive influence of family members while in the study. Several participants discussed the active role those family members had on steering their behaviour by wearing the footwear and insoles. As two of the participants suggested:

> “My wife has to tell me to take them off when I go out because I forget. She says, ‘go change your shoes’.” (0114)

> “I have got a pair of slippers, but I normally walk around with nothing on my feet. She (wife) moans like ‘merry hell’ at me.” (0203)

The support and awareness provided by family members with general diabetes care can similarly encompass participants’ general health and wellbeing. One of the patient participants gave an example of a hypoglycaemic episode, which was managed by his wife, prompting him to seek medical care:

> “my wife said, so she knew was something not quite right” (0208).

The support afforded by participant’s relatives extended to non-health issues associated with study participation. One of the participants disclosed his

struggles to read and write and the impact of this on his life. However, he highlighted the support of his family, and specifically, how his wife assists his reading and in particular for help in completing the study questionnaires:

> "The wife would read it to me because I am not a very good reader." (0203)

6.4.2.4 House shoes

The use of the house-shoes and insole provoked further comments by many patient participants, with particular usage habits highlighted. Many participants described behaviour routines related to wearing the house-shoes and insoles indoors, not considering them as suitable to use outside of their home environment:

> "Tend to use them mostly when I'm in the house for any length of time or sort of, when you first get up in the morning and things like that." (0318)

> "I probably haven't been wearing the shoes for as long as the trialist would want me to, because a) they're indoor shoes, and b) I'm always going out and putting on walking boots for taking the dogs for a walk. And I certainly wouldn't walk into town or outside with them (the house-shoes)." (0315)

The functional aspects of the house-shoes raised considerable attention from the participants. Some patient participants described issues related to ill-fitting house-shoes which caused them to be apprehensive about wearing them, with occasional tissue damage caused:

> “They tend to like slip off, don’t matter how tight you pull it! They are…they are not close fitting enough for my liking.” (0110)

> “My feet slop in them a bit, and I think that’s what leads to the sensation of me sliding off the insoles sometimes or sliding off the heel pad…. really the right foot and that was where I’d obviously, when I fastened the back, I’d not covered all of the Velcro and the Velcro rubbed on the skin.” (0318)

6.4.2.5 Study support

All patient participants highlighted the positive impact of the professional support provided by the podiatrist during the delivery of the trial procedures. Reassurance, receiving an explanation of the study process and being given time to understand the description were all contributory actions that created a supportive relationship between the podiatrist and the participant. One participant highlighted their initial interaction with the podiatrist:

> “When I got there, they made me very welcome. They explained to me what they were going to do and didn’t rush anything, and it was very good. She sat me on that couch and explained everything to me about what they were going to do; what they did.” (0205)

6.4.2.6 Podiatrist networks

The three podiatrists spoke of the positivity of the collaborative networking that was associated with their involvement in the study. The networking was provided by the research team and the study podiatrists and proved helpful in

providing operational support when required. As one of the podiatrists highlighted:

> “Good to highlight the team. I knew a few of them, but it was good as you can get contact numbers so that you could discuss things between each other it’s a good way of networking in the research team.” (01P)

The podiatrists highlighted areas where the support could have been improved during the study. As an example, one of the podiatrists highlighted a particular area associated with the plantar pressure collection process:

> “Just a bit of reassurance if somebody could have sat in and said yes you’re doing it right, so there were a couple of things with the Fscan, and I wasn’t entirely sure if I was doing it right and I checked the manual, and it wasn’t defined in the manual so, yes maybe a little bit more support actually in the actual data collection side of things.” (02P)

The provision of support to enable the self-affirmation of competence, especially in areas of clinical uncertainty, may provide the podiatrists with opportunities to improve the delivery of the study protocol.

6.4.2.7 Training

The training package, which consisted of the instruction manual and face-to-face training, provided reassurance to support the delivery of the study procedures for the podiatrists. One podiatrist suggested the instruction manual was acceptable, highlighting that it was:

> “Very clear and precise, nothing came up in the study that wasn’t in there, I think that tells it all really yeah nothing come up that I thought I don’t know how to do this.” (01P)

Another podiatrist reported explicitly on the instruction manual and its usefulness during the delivery of the study intervention. They found that the manual provided a step-by-step guide that was easy to understand and refer to for information to deliver the intervention. They also found the insole algorithm printed onto a laminated sheet as a poster was easy to refer to and provide assurance that they were following the correct process when delivering the intervention:

> “Yes, that was very useful, I refer to it all the time because there was quite a gap between each participant, and I would find that I had to go back to the instruction manual because I forget (laugh) to do things or what do I do here, especially the criteria for what to do with the insoles and the ‘Stomping gait’, that was really useful and very clear, nicely and visually laid out that you could look at it; that laminated sheet you could look at it quite quickly and see what category the patient fell into. Yes, it was quite clear and easy to use.” (02P)

However, each podiatrist identified areas that could be modified to improve the training session. In particular, there were suggestions of more time for questions and answers and the introduction of a scenario as part of the face-to-face training:

> “Yes, the training session was good really enjoyed it, and well delivered and I think probably there were lots of questions I didn’t ask that maybe I should have. Um, I think what might have been helpful for me was to do a scenario there, after the training had been delivered.” (03P)

6.4.2.8 Participant interaction

All podiatrists reflected on the positivity of the patient participant interaction during delivery of the study procedures. Each podiatrist alluded to the awareness of the participants’ behaviour and engagement, specifically a desire to understand the processes associated with manufacturing the insole. This awareness allowed the podiatrists to explain their clinical reasoning and provide increased support to the study participants with diabetes, giving an increased sense of job satisfaction:

> “From a patient point of view, it’s good for us to use it as a tool to show them what we are doing and make it more understandable. I found all the participants to be willing and able, all very pleased and happy to take part.” (01P)

> “They’ve been, yeah, really interested in what we’re doing as well, so I enjoyed the longer time with the patients, interaction.” (02P)

> “The patients were very appreciative of it; the ones that we had hadn’t had anything at all so you’re offloading them. I think they were very positive about it because it was part of the trial whereas normally you give a patient an insole and you know, sometimes they’ll take it home and wear it and sometimes they’ll go and stick it in the bin won’t they, so

I think they interacted with it a lot more because they saw it as more important.” (03P)

6.4.3 Impact of study involvement

This third theme is named ‘impact’ and describes the impact of study involvement for the patient participants and podiatrists. The impact theme relates to factors arising from patient participants and podiatrists contributions to the study. Four sub-themes emerged from the patient participants interviews: location and logistics, diabetes impact, overall experience, and receiving the study results (Table 6.2). Three sub-themes emerged from the podiatrists' interviews: overall participation, change in practice, and dissemination (Table 6.3).

6.4.3.1 Location and logistics

The location and logistics to attend the clinic for the study interventions were highlighted as impactful by many of the patient participants. Some participants had to travel to clinic sites other than their usual treatment place to be involved in the study. This travelling resulted in additional exertions to access the clinic location, as two participants highlighted:

“Gives me a day out really, a ride on the bus and the boat, but that’s the only thing.” (0208)

“It wasn’t the appointment; it was the flipping traffic getting there.” (0316)

Despite the variety of efforts to access the clinic location, many of the patient participants used the opportunity to see the travel to a different clinic site as a

positive experience:

> "I live, what, 20 minutes away. It doesn't take me long to get here; it's an adventure." (0116)

The clinic location is an important issue for many patient participants and must consider their potential requirement to use a variety of using various transport methods, despite the positive attitude of many participants. Other factors were influential on attendance, as two participants highlighted:

> "I think I went in February that month; I said if the weather is really inclement, I wouldn't risk coming if it were snowing or things like that" (0208)

> "No, the first time it was a bit of a shock because it was so bloody cold, pardon my French! It was sort of February March time, and it was so cold and that floor in there was absolutely freezing." (0103)

6.4.3.2 Diabetes impact

The impact of living with diabetes on patient participants' lifestyles and behaviour was deliberated by all participants. There was widespread recognition of the importance of diabetes management. In particular, diet and food choice were frequently discussed, as one participant highlighted:

> "It's just that I've got to be careful about what you eat and what not." (0202)

Often the motivation to engage with diabetes management activities was linked with a desire to prevent foot complications associated with diabetes, as several participants highlighted:

> “My biggest worry is that they suddenly start chopping your toes off, which I know that they do. Because a friend of mine had to have two or three toes off for that reason because she lost the feeling in them.” (0205).

> “I said to you earlier, so many people you hear now lose toes and God knows what else.” (0307)

6.4.3.3 Overall Experience

Patient participants highlighted a range of experiences related to participation in the study. Many participants reported enjoyable experiences, often associated with improvements in their foot health, as one suggested:

> “To be negative about it, I would say there are no negatives as far as I am concerned, that might sound you know good or bad I don’t know. From my perspective, it’s worked 100%.” (0307)

Other participants suggested improvements to the study. In particular, the use of a wireless system instead of cable for in-shoe measurement of foot pressure was one way of improving the study experience:

> “Perhaps one day you won’t have to use all those wires and that. Do you know what I mean? Perhaps the old computer could do exactly the same job, do you know what I mean because it looked a bit old fashioned.

> Connecting you up to all those cables like they got now, but it done the job, really good!" (0205)

6.4.3.4 Sharing study results

The importance of sharing the study results was evident in the views of all the patient participants. Many demonstrated a high level of interest and spoke of the desire to be informed of the study's outcomes. In particular, to receive the study results and to understand the impact and implications of the contributions from their involvement, as one participant highlighted:

> "Because by the end of the 12 months, we'll have developed a relationship with the project and all of the team here that are doing the maintenance with the feet. You know, so it would be nice to have, I don't know, five minutes in a room where you can say we've proved it by doing that." (0116)

In addition, some participants wished to establish which treatment insole (active control or intervention) they had received as part of the study procedures. One participant highlighted:

> "Well, purely out of interest because you've been involved in something, it would just be interesting to know a) If I've got the real one or not and b) whether the trial proved that there is an area there that can be improved if we do whatever, or there is scope for improvement." (0208)

There were various suggestions provided by the patient participants on how to share the results of the study. Some participant's highlighted written material as

being useful for providing this information, as one suggested:

> “It would be nice to, if it was em, personalised, you know, the simple bit of paper or something like that. Not too technical, but just briefly explains what we’ve done, and this is where or how you participated. Just general feedback.” (0114)

While others expressed preferences for receiving a more formal presentation, as one highlighted:

> “I mean I wouldn’t be averse to attending if you did like an afternoon seminar or something on the research findings, I’d be more than happy.” (0318)

6.4.3.5 Overall participation

Each podiatrist voiced a positive impact as a consequence of their participation in the study. They all appreciated the opportunity to be involved in delivering a clinical study and the self-development that occurred, as one of the podiatrists highlighted:

> “and just being part of the research process as well being able to see things from your perspective as well and understanding about how to pitfalls about setting up a project and I’ve done research myself but not on this sort of large scale, so that’s been really interesting as well.” (02P)

The podiatrists also voiced constructive comments about how the study had given them optimism for the future progression of the podiatry profession, as one podiatrist highlighted:

> “So yeah, I found that bit nice and enjoyable and also I think it gives me hope for podiatry in that we’re using new technology and equipment and not just set in our old bold ways.” (03P)

6.4.3.6 Change in practice

All podiatrists reported impacts of change to their clinical practice as a result of involvement in the study. In particular, the impact of the Fscan and insole algorithm had altered the clinical reasoning and insole design that they provided to existing patients, as each highlighted:

> “it’s really good and positive to have a quantitative measure to be able to see what you’re doing; it’s really positive in that respect because it gives you instant feedback, that you’re doing something good.” (01P)

> “Yeah, it’s made me stop and think about what we do, you know you’ve just got you, you do things out of habit a lot of the time because that’s how you’ve always done them. And then you use the F Scan and you suddenly think oh, actually that’s not doing what you expected it to do.” (02P)

> “But it certainly changed my practice. I think the main thing was looking at numerically how your practice changes things, and being able to see it on the screen is more powerful than just sort of issuing an insole and then go away and come back again. I find that I use some of the designs of the insoles in my normal clinic now when offloading certain joints and it’s had a good effect. So yes, I’ve learned a lot.” (03P)

Interestingly, none of the podiatrists commented on the clinical restriction of having to follow the insole algorithm, but rather embraced the impact on their clinical practice.

6.4.3.7 Dissemination

All podiatrists were enthusiastic about being given the study's results and the conclusions. However, each podiatrist viewed the dissemination of the results in a different way. One of the podiatrists desired written feedback on the study outcomes, highlighting:

> "For me, I just want a simplified paper, yeah, just a nice little abstract. Well, actually, some of the participants would like feedback so just a really quick, you know methods and the results done nicely and graph format. Conclusions, obviously, what you're going to take forward." (01P)

Another podiatrist felt it essential to disseminate the study outcomes to the podiatry team in a training session so that they could benefit from the study as suggested:

> "I would like to discuss the findings with the team. I don't know if you'd be happy coming down and presenting your findings to the team but I think that would be amazing to show clinicians who have been involved in it." (03P)

6.5 Summary

This section summarises the three main themes and subthemes. It presents the underpinning principles of every theme derived from the interviews of patient

participants and podiatrists and related to the third study objective.

6.5.1 Principles from the accepting of study methods

Overall, the accepting of the study methods theme provided reassurance that the study procedures were acceptable to patient participants and podiatrists. Sub-themes identified specific elements of the study procedures that were acceptable and identified areas that required improvement for a potentially future, larger RCT.

Involvement in the study and the randomisation process was acceptable to most patient participants. However, some deemed the PIS as lengthy and easy to forget its content. Participants raised issues about some aspects of the questionnaires' content, although completing them was acceptable. Patient participants presented a variety of perspectives related to wearing the house-shoe and insoles. Some highlighted determinant factors related to use, such as when indoors, and there were frequent concerns raised about the house-shoe's safety. Most patient participants found the assessment process for receiving the footwear and insoles as acceptable, apart from difficulty during the calibration task. Podiatrists highlighted the provision of the house-shoe and production of the insole as straightforward, although safety concerns were raised over the house-shoe. Improvements to address the concerns of the podiatrists relating to the technical constraints imposed by the NHS IT systems and site recruitment targets are required for future study design.

6.5.2 Principles from behaviour and support during study procedures

The behaviour and support during the study procedures theme revealed different insights into the patient participants' experiences and podiatrists' conduct during the study period. This theme highlighted factors that influenced patient participants and podiatrists' actions and experiences during the study.

Sub-themes identified diverse patient participant's behaviours of self-foot-care activities, which can influence foot ulceration risk within the study. Different motivations influenced the decision to participate in the study. Some patient participants had altruistic motivations while others hoped they were receiving improved treatment for their foot care. Some participants highlighted the supportive contribution of family members and how this influences actions relating to using footwear and insoles and managing their diabetes condition during the study. The support provided by podiatrists was emphasised as an essential factor in participant recruitment and enabled a positive experience for patient participants. Podiatrists were equally cognisant of the positive interface with the participants during the study. They related the satisfaction of having the time to explain the study processes to participants. Podiatrists also revealed the influence of a supportive network from the research team. This support complemented the training program to deliver the study procedures, although some modifications would benefit the anticipated future study.

6.5.3 Principles from impact of study involvement

The impact theme of study involvement revealed different aspects of the study that were impactful on the patient participants and podiatrists. Embracing the

positive impacts and addressing the unconstructive impact elements will assist with key study variables, such as participant recruitment, retention, and adherence to the intervention. It will also help guide the dissemination of the study results to be impactful in the public, clinical and academic areas.

Sub-themes revealed the impact of the clinic location and the struggles that some patient participants had in accessing the location, which is an important consideration for the anticipated larger study. They highlighted the impact of living with diabetes and how this is frequently motivated by a fear of foot ulceration and amputation. This impact influences participants' conduct and could affect foot ulceration risk. Overall, participants enjoyed taking part in the study finding it interesting and not burdensome which is important to recruitment and retention rates. There was a common desire to receive feedback about the study outcomes, although the preferred mode of delivery for the dissemination varied amongst the participants with diabetes. A sub-theme relating to overall learning was highlighted by the podiatrists, who reported impacts of positivity and enjoyment from their contribution to the study. They highlighted the impact of the changes in their clinical practice due to their involvement in the study and recognised the influence that dissemination of the study results could have on their colleagues.

6.6 Chapter summary

This chapter has presented the findings from the qualitative study embedded within the INSTEP fRCT. Three key themes were identified from the patient participants' experiences of receiving the intervention, and podiatrists' experiences of delivering the intervention. Analysing the themes and contextual

findings in combination with the results from the quantitative RCT, will provide recommendations for the anticipated future RCT, will be discussed in the next chapter.

Chapter 7 Discussion

This chapter provides a discussion of the thesis, the aim of which was to develop and test, in a feasibility randomised controlled trial (fRCT), an insole prescription and fabrication intervention appropriate for chairside delivery to reduce plantar foot pressures in people with diabetes. Using the MRC's framework for developing and evaluating complex interventions, the first phase of the research developed a novel optimised insole, informed by stakeholder and patient/public involvement and a systematic review with three meta-analyses. The second phase involved conducting a multicentre fRCT with an embedded qualitative study. The fRCT aimed to obtain the necessary data and operational experience to finalise the planning of an intended future definitive multicentre RCT to compare the optimised insole and usual care with an active control insole and usual care for people with DPN. The intention was to determine if the trial should proceed to a definitive trial and learn lessons to enable a definitive trial to be successfully delivered with confidence.

The discussion is a convergence and interpretation of the results and findings from the different phases of this research in context with the broader literature. Specific learning points related to the research objectives are presented, with recommendations for the definitive anticipated RCT presented in the next chapter.

7.1 Developing and testing the intervention

Informed by the MRC framework for developing complex interventions, the optimised insole was developed to reduce the risk of DFU in people with DPN.

Proof-of-concept work, a systematic review and stakeholder engagement informed the theoretical construct which underpinned the development of the optimised insole algorithm. Using such a structured approach enables the optimised insole intervention to be reported according to the TIDieR checklist which assists with transparency and future replication (Hoffmann *et al.*, 2014). However, whilst the MRC framework enables a flexible approach to intervention development and is well cited in the literature, other more prescriptive approaches to intervention development are available. For example, a taxonomy of approaches to intervention development classifies eight categories of approach (O'Cathain *et al.*, 2019). Therefore, other approaches to complex intervention development are available, although context, needs and values will determine which approach best serves the developer's purpose.

By nature of its status as a fRCT, the clinical and cost-effectiveness of the optimised insole in reducing MPPP and reducing the risk of DFU is not able to be determined by this work, although a signal of efficacy suggests that this is plausible. Clearly defining the signal of efficacy is challenging given that it is an imprecise estimate (NIHR, 2019a) and that no definitive MPPP magnitude at which DFU occurs. An inferential link is instead required that the within-group differences in MPPP is clinically important in reducing the risk of DFU. In conjunction with the between-group estimates of MPPP change, there is an expectation that the MPPP reduction with the optimised insole is clinically important at all ROI's until six-months. This warrants further investigation to add to the existing evidence-base, although the complexity of the causal pathway for DFU suggests that information pertaining to MPPP reduction should be

interpreted within this context rather than being treat in isolation. In reality, the multi-factorial nature of DFU, demonstrates that even though the optimised insole may reduce MPPP and foot ulcer risk, its impact on reducing diabetic foot ulcer incidence may not be guaranteed. This is because many of the incurred diabetic foot ulcers were not related to elevated plantar foot pressure but to extraneous traumatic events (such as standing on a nail) which are not attributable to the complex causal pathway of DFU or the intervention. The frequency of diabetic foot ulcers in this study is similar to proportions in other studies, such as Abbot et al (2019) who reported 49.0% related to trauma and ulceration unrelated to the intervention and 11.8% related to falls (Abbott *et al.*, 2019).

The complexity of the components that characterise an intervention is a common problem in the development and evaluation of complex interventions that can frequently result in uncertainty in its ability to act as predicted (Levati *et al.*, 2016). Within this study, for example, there were multiple factors that all have the potential to influence the outcome. Consequently, interpretation of any outcomes is complex and could be better evaluated using process evaluation. Key was the participants' adherence to wearing the house-shoe and insole. For instance, participants spoke of the influence that family members guiding their behaviour in using the house-shoe and insole intervention. This is in line with the literature that shows that family and friend's support is closely related to the self-efficacy level of people with diabetes (Rosland *et al.*, 2008) and maintaining lifestyle changes and optimizing diabetes management (Rintala *et al.*, 2013). Furthermore, higher social support levels are associated with improved clinical

outcomes in people with type 2 diabetes (Strom & Egede, 2012). Similarly, living with the threat of developing DFU and lack of perceived control underpins emotions and behaviours for people with DPN. Emotions and behaviours are an essential determinant of foot-care practice, influencing DFU outcomes (Vedhara *et al.*, 2014). Some participants highlighted that fear of developing a diabetic foot ulcer prompted a more positive approach to foot-care self-efficacy, whilst others were less engaged. Quantifying adherence and self-care practice levels amongst participants for the future RCT and analysing if there is an effect on the primary outcome between intervention groups will therefore be important.

Overall, the findings relating to the delivery of the optimised insole were positive, although some safety concerns around falls and rubs with wearing the house-shoe was conveyed by both the podiatrists and participants. Overall, the delivery of the house-shoes and insole interventions by the three podiatrists were acceptable in terms of following the optimised insole algorithm. The optimised insole intervention met some of its clinical aims, by using real-time plantar pressure data to inform the design and fabrication of a chairside insole, using commercially available materials, provided at the same appointment. However, uncertainty of the clinical benefit of providing the Pulman-house shoe remains as it was not tested in this study. Whilst the house shoe provided the opportunity to standardise the measurement of the effect of the insole, participant feedback was varied on its use as a therapeutic shoe. The use of the house-shoe in this study was to provide a choice of footwear for participants when at home and while waiting for the provision of therapeutic footwear, which is often considered for outdoor use only (Paton *et al.*, 2014a). It was anticipated

that this would increase the opportunity for participants' feet to be protected by wearing prescribed footwear and insoles, as opposed to barefoot or slippers (Cavanagh & Bus, 2010). This was highlighted in a previous study which demonstrated low adherence to wearing therapeutic footwear and insole at home, compared to outdoors (Waaijman *et al.*, 2012). By not evaluating the use of the Pulman-house shoe compared to usual care, its value as part of the study intervention is uncertain.

One area of dissatisfaction highlighted by the podiatrists was frustrations with the availability of technical support, which appears a recurring theme in other studies and in clinical practice. Perceived obstacles associated with inaccessibility to IT support systems and software problems are the most commonly reported technology issues within the National Health Service (Kim, Coiera & Magrabi, 2017). Similarly, a qualitative survey amongst UK practitioners prescribing customised foot orthoses within the NHS identified barriers to the use of technology in clinical practice, including usability issues and lack of training (Williams *et al.*, 2016).

The process for receiving the insole by patient participants was acceptable in terms of time taken to receive the intervention but provoked emotional responses, such as apprehension, for some participants. This was frequently managed by the podiatrists' support and was cited as being vital to both podiatrists and participants in providing a self-affirmation of their actions. Using clinical skills to keep the patient participant engaged and feeling respected are other positive engagement strategies experienced from behavioural intervention studies (Olem, Sharp & Johnson, 2009). Studies that contain collaborative,

trusting relationships and effective communication strategies report positive impacts on quality of care and successful patient outcomes (Brown *et al.*, 2016). Therefore, encouraging and stressing the importance of maintaining positive interactions should be an important consideration in the successful implementation of a future RCT.

In this study, there was excellent fidelity when delivering the insole intervention (Horner, Rew & Torres, 2006), and good to high test-retest reliability of the determination of MPPP (Atkinson & Nevill, 1998; Koo & Li, 2016). Standardising the delivery of the intervention is critical to maintaining the internal validity of any study. Excellent fidelity to the intervention delivery, and reliable determination of the MPPP could be attributed to the training package and the support network that the podiatrists accessed during the trial procedures' delivery, both sub-themes derived from the interviews. Although considered important features of intervention delivery in clinical trials, these elements can often be neglected (Roth, Pilling & Turner, 2010). The podiatrists highlighted that the training package was straightforward and easy to follow, although it is important to acknowledge that all the podiatry researchers were senior podiatrists who undertook insole manufacture and provision as part of their everyday clinical role. Consequently, it is possible that the training package may need to be adapted for less skilled clinicians in this area. The addition of a scenario exercise was proposed by the podiatrists to add further clarity to the training package. Active learning, which was the approach used for training in this study, and which includes clinical simulations, alongside practice and feedback have been identified as more effective educational techniques for health professionals (Beidas, Cross & Dorsey, 2014; Bluestone *et al.*, 2013).

The significance of a support network for clinicians to access is well documented as an approach to prevent fidelity deviations (An *et al.*, 2020). Furthermore, Farrell (2010) suggests a crucial step to undertaking a successful study is to create a collaborative group of interested individuals that enables involvement and ownership, although time and commitment remain barriers (Farrell, Kenyon & Shakur, 2010). In this study, the support network may have further benefitted from following a structured approach, such as the clinical supervision framework. Clinical supervision practices can significantly improve performance, as reported in a systematic review across a range of health professionals (Snowdon, Leggat & Taylor, 2017).

Closer examination of the reasons for the protocol deviations in this study revealed that the majority were related to research capacity and operational constraints at each site. Understanding the cause and frequency of protocol deviations provides an indicator of the extent to which the insole intervention was delivered as prescribed. Research capacity and operational barriers remain a common problem for undertaking research within the NHS setting. The demands of clinical service provision, such as appointment capacity, often relegate research activities to a secondary position. Although protocol deviations are expected in the delivery of a complex intervention (Ermete, 2012) with varying degrees of impact, (Mehra *et al.*, 2014), anticipating such issues and providing solutions to improve the delivery of the intervention which would be an important consideration when designing a future RCT.

7.2 Study procedures

One objective of a feasibility study is to assess the effectiveness of the study procedures in preparation for the anticipated RCT (Tickle-Degnen, 2013). Acceptability of study procedures contribute to the success of clinical trials (Fogel, 2018). In this fRCT, recruitment failed to reach its target, recruiting 61 out of the target of 76. However the rate of recruiting eligible participants of 43% was similar to other UK RCTs investigating insoles for people with DM of between 44.2% and 61.7% (Abbott *et al.*, 2019; Parker *et al.*, 2019). This was despite the introduction of several recruitment strategies in an attempt to reach the projected sample size (Treweek *et al.*, 2013). Recruitment to multi-centre RCTs can be particularly challenging, with a survey of UK clinical trials reporting participant recruitment as the most common inefficiency (Duley *et al.*, 2018). Furthermore, not meeting the planned sample-size is commonplace, as reported in a review of RCTs funded by the UK NIHR Health Technology Association Programme which found that only 56% of publicly funded RCTs achieved this (Walters *et al.*, 2017). Subsequently, recruitment in this fRCT has been valuable in determining a more realistic rate and identifying further recruitment strategies for the definitive RCT.

The value of a personal invite by podiatry clinicians in recruiting participants to the study was a particular sub-theme identified from the participant interviews. Being asked to participate in the study was a key reason as to why people said they enrolled in the study. Therefore, it will be necessary for a future large-scale definitive trial to include measures to facilitate engagement and active involvement from podiatry team members at all sites to optimise recruitment.

This concept is supported by thematic analysis of data from focus group discussions of clinicians in a UK-based multi-site RCT (Skea, Treweek & Gillies, 2017). The authors emphasised the necessary engagement to ensure that clinical staff were both educated and motivated to help with the process of identifying and screening potential prospective participants to the trial. Part of this engagement could encompass describing the motivations for participants to join the study, which may assist podiatry clinicians when approaching potential participants. The patient participant interviews in this study revealed contradicting motivations of altruism and self-benefit as reasons for participation, which are reported in other studies involving people with type 2 diabetes (Estcourt *et al.*, 2016). However, the podiatrist interviews revealed that they struggled to engage other podiatrists within their service to identify participants as part of the recruitment process. Speculatively, there is a gap in knowledge about the best ways to engage with the podiatry clinicians. One systematic review (2018) suggested that the clinician time burden could be partly responsible for the lack of engagement (Treweek *et al.*, 2018). Another author expounded on the role of enthusiastic PI's in multiple sites to help realise timely and complete recruitment in clinical trials through engagement (Thangaratinam & Khan, 2015). Although not formally evaluated within this study, the CI's role in engaging and motivating podiatry clinicians could be attributable to the variations in recruitment rates across sites, since recruitment rate was notably higher in the Trust where he worked.

Recruiting fairly and equitably across populations of potentially eligible individuals is important to ensure the external validity of clinical trials. Almost all

of the demographic characteristics in this study are similar to other studies investigating insoles and prevention of DFU in people with DPN. In terms of age, values are comparable with other UK epidemiological studies in Nottingham (Ince *et al.*, 2007), and Devon (Paisey *et al.*, 2018). Other participant demographics relating to BMI, diabetes type and duration of diabetes were equally comparable with other diabetic foot ulcer prevention studies investigating footwear and insole interventions (Abbott *et al.*, 2019; Parker *et al.*, 2019; Paton *et al.*, 2012). Therefore, these participants can be considered a good representation of people with diabetes and at risk of DFU.

However, gender and ethnicity appeared unrepresentative of the general diabetic population. In this study, 86.9% of participants were male, suggesting an over-representation considering other UK cohort DFU studies report the proportion of males as 62.0% in Nottingham and 69.9% in Devon (Ince *et al.*, 2007; Paisey *et al.*, 2019). Yet other UK RCT studies involving insoles for people with DPN have reported similar proportions of gender ratios (Abbott *et al.*, 2019; Parker *et al.*, 2019), suggesting struggles to recruit female participants. All the participants in the current study identified with white ethnicity. This suggests that the ethnic status proportions in this fRCT is not representative of the population with diabetes in the UK where an observational cohort UK study of type 2 diabetes (2004-2017) reported 63.4% were of white ethnicity, 3.9% South Asian, and 1.6% black (Mathur *et al.*, 2020). Furthermore, Type 2 diabetes is associated with higher prevalence in Asian and Black ethnic groups (Pham *et al.*, 2019) and subsequent DFU, as reported in a US/UK dialysis-treated diabetes cohort (Ndip *et al.*, 2010).

There is often an under-representation of ethnic minorities in clinical trials (Redwood & Gill, 2013). The exclusion of specific patient populations may lead to impaired generalisability of results (Van Spall *et al.*, 2007). Cultural and language barriers are often cited as reasons, although solutions to overcome these challenges are not easily accessible. Yet, not addressing this imbalance and recruiting a truly representable and generalisable sample to the population under investigation introduces bias (Gyure *et al.*, 2014) and risks the intervention not being relevant or accessible to those vulnerable and hard to reach populations who need it most. Recruiting a Black, Asian and Minority ethnic representative and a female patient and public representative to be part of the trial management group is one useful strategy for the future trial.

Within this study, the participant completion rate was slightly below the target of 70%, which was comparable with similar studies investigating insoles for people with diabetes (Parker *et al.*, 2019; Paton *et al.*, 2012). Reducing study attrition in studies is important in enhancing the internal and external validity of findings (Page & Persch, 2013). One way of reducing attrition and loss to follow-up in clinical trials is to maximise patient appreciation (Fogel, 2018). This was reflected in the comments of participants in this fRCT, who highlighted the importance of the podiatrists' support as heavily influencing their positive experience of participating in the study. The value of a supportive relationship can enhance retention in studies, as shown by a cross-sectional qualitative study of (NIHR HTA) portfolio of ongoing UK trials during 2014 (Daykin *et al.*, 2018). The authors conducted semi-structured interviews and reported that trial staff who interacted with participants placed great value on maintaining contact with participants and interpersonal relationships to enhance retention. This

relationship can often overcome the barriers to non-attendance (Brewster *et al.*, 2020).

The reasons provided for withdrawing from the study were variable, making it difficult to infer any conclusions about why this might be the case. Some clear sub-themes emerged from the interviews with patient participants that could have influenced participant retention in the study. Practicalities such as time commitments and geographical location were prominent in highlighting participants' ability to commit to trial participation. Many interviewees indicated other time commitments that could impinge on attendance and accessibility of the clinic location. Some patient participants highlighted concerns over the inability to drive their motor-cars, associated with diabetes-related problems, while others reported using several different public transport methods to access the clinic. These factors are particularly relevant to elderly patients, as reported by a study examining patient recruitment and retention in the diabetic population (Ory *et al.*, 2002) and a systematic review examining the reasons for non-attendance for out-patient appointments by people with DM (Brewster *et al.*, 2020).

Other authors make suggestions for improving participant retention in clinical trials. A synthesis of qualitative data from 11 studies highlighted that providing more detail on the nature of the trial interventions and what can be expected by 'participation' at the consenting stage may help manage expectations (Skea, Newlands & Gillies, 2019). With many people citing altruistic reasons for participation, practical strategies to improve retention may include improving

participants' understanding of treatment equipoise, the importance of outcome data collection and follow-up, regardless of treatment adherence (Kearney *et al.*, 2018). A previous qualitative study recruiting adults with type 1 diabetes found that factors relating to volume, clarity and consistency of information were all cited as influencing trial retention (Henshall *et al.*, 2018). Within this feasibility study, patient participants remarked on the comprehensive information provided within the participant information sheet, although some felt it was too long.

All of the podiatrists reported the constraints of time as an issue to delivering the study procedures efficaciously. This sub-theme is a constant reminder of the conflicting demands between clinical and research workloads (Farrell, Kenyon & Shakur, 2010). "Lack of time" has been identified as the most common barrier to clinicians participating in research (Rosland *et al.*, 2008). Creating an optimal balance between the clinical workload and the research methodology is crucial to any study's success (Johnson & Remien, 2003). However, the implicit culture remains in most organisations where clinicians and managers see clinical care and evidence-based practice as independent activities, with one perceived as more critical than the other (Harding *et al.*, 2014).

Analysis of demographic data can help to determine if the randomisation procedures were successful, thereby minimising the impact on the study outcome (Spieth *et al.*, 2016). In this fRCT, the medical history and clinical variables were comparable between the active control and optimised insole groups, indicating that the randomisation by stratification procedure was appropriate. Additionally, the participants' medical history was consistent with

those of previous studies involving insoles and people with DPN, wherein medical comorbidities, such as cardiovascular disease, were the most frequent reported (Petrie, Guzik & Touyz, 2018; Walsh *et al.*, 2016). Half-of-the participants had a history of previous DFU, which is almost identical with Parker et al.'s (2019) study of similar pragmatic design (Parker *et al.*, 2019). A history of previous DFU could be considered as a confounding factor due to its association with higher foot plantar pressures than those without a history of DFU, potentially increasing the risk of DFU (Ledoux *et al.*, 2013). Therefore, establishing the proportions of those with a history of DFU is important for analysis purposes and should be considered for stratification in a larger trial.

Forefoot deformity and lack of joint mobility are associated with an increased risk of developing a diabetic foot ulcer located on the plantar surface of the foot (Cowley *et al.*, 2008). In this fRCT, over-half of the participants had some form of foot deformity and joint mobility limitation, which was similar in comparison to other studies involving insoles for people with DM (Burns *et al.*, 2009; Paton *et al.*, 2012). Additionally, most of the combined regions of interest (ROI's) were located in the forefoot region, which is also consistent with other studies within this field (Arts *et al.*, 2015; Bus, Haspels & Busch-Westbroek, 2011). Interestingly, very few studies involving the provision of therapeutic footwear and insoles to reduce the risk of DFU have recorded foot deformity and range-of-motion (ROM) in any depth. This appears an omission, especially considering that foot deformity and joint mobility limitation are considered a contributory step in the causal pathway to DFU and an indication for therapeutic footwear and insoles. Subsequently, in the absence of standardised measures

for foot deformity and ROM for studies involving people with DPN, the future development of related guidelines would address the gap in the literature.

Using a data logger gave an objective value of adherence to the insoles' wear time over extended periods of the study. Proportions of wear time were comparable with other studies that also measured adherence using sensor based technology (Abbott *et al.*, 2019; Waaijman *et al.*, 2012). This information is particularly relevant in people at risk of DFU, where review studies have described the under-adherence of wearing footwear and insoles prescribed for offloading (Bus *et al.*, 2008; Bus *et al.*, 2016; van Netten *et al.*, 2020b). Most studies to date have used self-reported methods to measure adherence to footwear and insoles for people with DPN, either by questionnaire (Arts *et al.*, 2014; Churchman, 2008) interviews (Chantelau & Haage, 1994b; Kossioris *et al.*, 2017) or monthly telephone call (Parker *et al.*, 2019). These are considered weaker measurement methods, due to patient over-reporting, than objective measure methods (Jarl, 2018).

The advantage of objective measurements is that it gives a more reliable indication of adherence for the duration of the study. Data loggers enabled an absolute measure of adherence for more extended periods, rather than a snapshot representing the study duration. However, variations in wear time according to activity, season and time of day were not analysed at this level of detail. A longitudinal study in the US concluded that day of the week, month and weather had modest effects on physical activity levels, as measured with walking steps of participants (Chan, Ryan & Tudor-Locke, 2006). Furthermore, the data logger only measured activity when wearing the insole intervention.

Although the use of the house-shoe in this study provided a choice for participants when at home, allowing the removal of therapeutic footwear considered for outdoor use (Paton *et al.*, 2014a), it did not capture the confounding effect of wearing other footwear and insoles. This implies a concomitant intervention as part of usual practice, which could reduce the external validity of the study (Bornhöft *et al.*, 2006).

The blinding process in studies involving insole interventions is notoriously challenging due to the difficulty in 'disguising' and concealing the intervention from participants, providers and assessors (Bonanno *et al.*, 2015). As in other studies the use of identical insole top-covers provided a credible alternative to the optimised insole, thereby enabling effective participant and assessor blinding (Paton *et al.*, 2012).

Patient participants in this study were keen to receive the study results, although the preferred delivery format varied. Dissemination of results to participants is heavily discussed in the literature, with some authors considering it ethically imperative (Taylor, 2019). One review found that only 10 out of 270 clinical trials presented explicit findings to study participants, of which six were through a lay summary or letter (Raza, Bruhn & Gillies, 2020). The podiatrists were also eager to embrace the impact of their participation in the study by embedding their experiences and skill development into their clinical pathways. However, despite the clear advantages of implementing research into clinical practice, substantial barriers remain. A recent metareview-synthesis reported that the most frequent obstacles to implementation are organisational (lack of a driver for implementation), clinician (lack of time of health professionals) and a

lack of clarity and credibility in the evidence for change (Correa *et al.*, 2020). Complementing this approach, other authors have highlighted the behaviour change of health professionals as the key to implementing evidence into practice (Francis, O'Connor & Curran, 2012). Slade et al.'s. (2018) review identified 16 research capacity-building frameworks that could overcome these obstacles (Slade, Philip & Morris, 2018). However, the large number of variables highlighted demonstrates the complexity of endeavouring to embed a research culture into allied health clinical practice, which in itself remains a barrier.

7.3 Outcome measures performance

Another aim of a feasibility study is to reduce threats to the validity of the study's outcomes by assessing the performance of the outcome measures (Tickle-Degnen, 2013). In this study, there were high completion rates of the proposed primary outcome measures of MPPP and photographs to assess incidence of DFU, for all baseline data sets and for those who attended the follow-up sessions. There was similarity in outcome measure performance between the control and optimised insole groups.

In this fRCT, the proportion of participants incurring a diabetic foot ulcer are comparable to epidemiological studies where the lifetime incidence of DFU for people with DM is estimated at between 19% and 34% (Armstrong, Boulton & Bus, 2017). More pertinent for studies, such as this one, where the study populations are a mixture of first and recurrent diabetic foot ulcers, recurrence rates are estimated at 40% within one year after healing, 60% within three years and 65% within five years (Armstrong, Boulton & Bus, 2017). However, in this

study there was no trend towards a difference in DFU between the optimised insole and active control groups. Jeffcoate et al. (2006) contends that traditional DFU related measures, such as healing rates, underestimates the true morbidity associated with DFU and their sequelae (Jeffcoate *et al.*, 2006). It is suggested that the effectiveness of care for people with DPN should encompass measures related to the person, as well as goals related to DFU (Pound *et al.*, 2005). Consequently, in the absence of core outcome measures for diabetic foot studies (Jeffcoate *et al.*, 2016), there is a trend towards using ulcer-free days as an outcome measure (Akturk *et al.*, 2019; Meloni *et al.*, 2020; Najafi, Reeves & Armstrong, 2020). Ulcer-free days are considered a marker for the effectiveness of management, as well as estimates of prevention and healing of complications of DFU, and would have been helpful to include in this fRCT.

Although this study was not designed to assess treatment effectiveness, reductions in MPPP were observed for both groups immediately post-randomisation compared to baseline. Other studies involving people with DPN have reported similar reductions in MPPP compared to baseline with a flat insole (Barnett, 2002; Birke, Foto & Pfiefer, 1999; Bus, Ulbrecht & Cavanagh, 2004) and custom insoles (Bus, Haspels & Busch-Westbroek, 2011; Paton *et al.*, 2012; Waaijman *et al.*, 2012). However, for both groups the performance of the active control insole and optimised insole throughout the study revealed considerable variations in the reduction of the MPPP compared to baseline. The active control insole showed gradual increases in MPPP compared to baseline for all ROI's at the follow-up time points. This contrasted with the optimised insole which showed variable MPPP reduction compared to baseline over the

follow-up time points. Other studies have reported similar performance issues with footwear and insoles when reducing pressures under the DPN foot. One RCT used a mixed-model analysis to report the reduced performance in reducing peak pressure and pressure-time integral at ROIs as the insoles became older (Hellstrand Tang *et al.*, 2014). They reported 57% of the insoles were changed due to excessive wear during the two-year study. A non-randomised study required further experimental insole modifications to preserve the effect of the pressure reduction achieved at issue (Waaijman *et al.*, 2012). The authors surmised that reductions in peak pressure for the optimised group could not be preserved in the short term (six months) without modifications to the insole at follow-up time points.

The variations in effect of the active control and optimised insoles to reduce MPPP throughout the study could be attributed to the insole materials. Insole materials can influence loading patterns and attenuate tissue stresses to the plantar aspect of the foot for people with DPN. The material properties will have an effect on the performance of the insole and its durability over time. The Poron and EVA materials used in this study for both insoles are those commonly used in the clinical setting and are considered suitable materials (Rome, 1991). In laboratory based tests, Paton and colleagues concluded that 3mm Poron 4000 had high dampening, good mouldability and low control properties when testing with cyclic loading (Paton *et al.*, 2007). In comparison, 12mm medium-density EVA demonstrated high control, medium dampening and low mouldability properties. Although this was not tested on participants or over a longer duration, Paton et al. (2014) reported that EVA insoles maintained their ability to reduce the magnitude of MPP over 12-months, despite showing

signs of physical deterioration (Paton *et al.*, 2014b). This contradicts the findings in this study, whereby there was a lessening effect of reducing MPPP of both of the insoles over time. This could be attributed to the materials fatiguing following high and repetitive compression loads (Faulí *et al.*, 2008) or an increase in barefoot MPPP over the duration of the study, although this data was not collected.

The Nottingham Assessment of Functional Footcare questionnaire (NAFF) (Lincoln *et al.*, 2007) and the International Physical Activity Questionnaire (IPAQ-short) (Booth, 2000) were used as patient-reported outcome measures (PROM's) in this study. The return rate and completion of the PROMS's was excellent and met the criteria set for progressing to a definitive trial. The proportion of postal questionnaires returned for both PROM's was consistent with other studies involving self-administered questionnaires for people with diabetes (Luckie *et al.*, 2007). The participant interviews highlighted that this high response rate could potentially be attributed to two factors: the podiatrists reminding the participant to complete the questionnaire when attending the appointment; and the acceptability of the PROM's format, style and time to complete.

The interviews also revealed that participants frequently had difficulty distinguishing between the response categories in the PROM's, especially for the IPAQ-short. This could be attributed to the generic rather than disease-specific features of the IPAQ-short. The absence of a PROM to provide a standardised method of obtaining participants' perceptions for people with

diabetes and foot and ankle pathology has previously been cited (Ortega-Avila *et al.*, 2019).

7.4 Strengths and limitations

A key strength of the work undertaken for this thesis is the development of an optimised insole utilising the MRC framework for developing and evaluating complex interventions. As such, it employed a collaborative and pragmatic approach to design the novel optimised insole algorithm to address key clinical problems associated with reducing the risk of DFU in people with DPN. Using a structured approach to intervention design can increase the potential for successful implementation and minimise the risk of subjects being exposed to ineffective interventions (Bleijenberg *et al.*, 2018). The use of a fRCT design with embedded qualitative study ensured a realistic assessment of capability to conduct a future RCT. The fRCT used well established validated outcome measures and met higher quality research criteria. Using multi-centres enabled the assessment of the intervention in different contexts (Craig *et al.*, 2018a). The semi-structured interviews followed established protocols and added significant insight into the experiences of patient participants and podiatrists in delivering and receiving the insole intervention. The results of this study were comparable to other studies involving therapeutic footwear and insoles for people with DPN and recommendations to inform a definitive RCT were achieved. The success in making recommendations to progress to a full RCT keeps entirely with the original aim of this study, and is acknowledged as having an important role in research (Blatch-Jones *et al.*, 2018). Moreover a signal of efficacy that suggests the optimised insole holds promise, although by way of

the fRCT design, it is not possible to determine whether an intervention is clinically or cost effective. This is frustrating when considering that another five years will be spent designing and implementing a definitive RCT, with an average of 17 years for new understanding and knowledge to be incorporated into clinical practice (Morris, Wooding & Grant, 2011).

In this thesis it is important to acknowledge the limitations that inevitably arise in research of this nature. The first limitation is the over simplification of the causal pathway to DFU. In reality DFU occurs through the combination of multiple, complex factors, where isolated interventions are frequently ineffective to reduce the risk of DFU. In addition, this study failed to explore cost-effectiveness, or trial these processes, which would have been helpful to include in preparation for the future RCT.

A further limitation of this research was the inability to distinguish the use of the intervention insole and Pulman house-shoe in concurrence with the participant's usual footwear. Although the decision to wear footwear and insoles is pragmatic in nature, this could introduce a confounding effect, whereby access to therapeutic footwear and insoles differ across sites.

Another limitation of this study is that the concept of different gait patterns requiring different insole designs, which is the basis of the optimised insole algorithm, has not been widely discussed in the literature. The optimised insole algorithm, is based on an intuitive concept, grounded on clinical experience that requires additional evaluation to verify the theory.

The lack of diversity amongst some of the baseline characteristics of the population recruited, which was not truly representative of the DPN population within the UK, is another limitation. All study sites were in the South West of England; therefore, behaviour and attitudes of participants and podiatrists are not representative of all podiatrists and people with DPN. There are other areas of the UK where there are significantly larger numbers of patients from different ethnic backgrounds. Generalisable studies, which use a conceptual framework approach to analyse all data from a diverse sample, can be considered the highest level of evidence (Daly *et al.*, 2007). This is considered important if the causal effects of the intervention on the study's population are truly generalisable to the real world setting (He *et al.*, 2020).

In the embedded qualitative study, only one female agreed to be interviewed, thereby limiting the transferability of the findings. This was in addition to undertaking the interviews after participants had completed the three-month follow-up appointment whilst they were still actively engaged in the trial. Therefore, the participant views were only representative of the early part of the study and not for the full study duration, and did not take into account the perspectives of those participants who dropped out of the study. The interviews were undertaken by the CI, where his presence during data collection, although unavoidable, can affect participant responses (Pope & Mays, 2006). Some participants also preferred their spouse to be present at the interview, which could also have influenced some of their responses. Even so, these findings can still inform current debates and recommendations for this fRCT.

7.5 Summary

This chapter has critically discussed the results and findings from the INSTEP fRCT in relation to its aims and objectives and in context with the existing literature. Recommendations will inform the next stage of the optimised insole design and full RCT, and these will be described in the next chapter, as part of the conclusion to this thesis.

Chapter 8 Recommendations for future research and conclusion

The focus of this last chapter is to summarise the thesis and present the recommendations for the design of the anticipated large scale RCT to test the optimised insole against an active control insole. It will then proceed to identify recommendations for clinical practice and future research and conclude the thesis.

8.1.1 Summary of recommendations from the feasibility study

The aim of a feasibility study is to obtain the necessary information and estimate important parameters needed to inform the protocol of an anticipated multi-centre RCT (Eldridge *et al.*, 2016b). Valuable insights and lessons have been learnt from undertaking this feasibility study, with recommendations developed. This section will summarise the recommendations from the INSTEP fRCT, which will inform a future definitive study to compare the clinical and cost effectiveness of an optimised insole with an active control insole for people with DPN.

8.1.1.1 Recommendations: Developing and testing the intervention

Overall the concept and delivery of the optimised insole appeared acceptable to participants and podiatrists, although recommendations to fine-tune these aspects are necessary (Table 8.1). With the study design meeting scientific rigour in terms of establishing the independence of the treatment effect, the signal of efficacy suggests that the optimised insole shows promise in reducing MPPP and should be investigated further. However, there are uncertainties over the durability of the insoles and their ability to reduce MPPP effectively for

longer than six months. This may necessitate the replacement of insoles for those participants at follow-up appointments, where MPPP is equal or greater than baseline, which would have cost implications for a future study.

The delivery of the insole intervention would be improved by addressing some of the operational constraints (appointment times and clinical locations) highlighted in the fRCT, although this will have implications on the study set-up. In particular, increasing study delivery time to incorporate administration time for the podiatrists and providing prospective IT support is recommended. The training package for the delivery of the insole intervention and study procedures demonstrated to be generally fit for purpose and could be used in the future study, with some relatively minor modifications which would have cost implications.

The importance of the positive interactions between participants and podiatrists during the study necessitates more formal recognition of supporting participants and their family and friends in conjunction with developing a structured support network for podiatrists during the study.

Table 8.1 Recommendation from developing and testing the intervention

Activity	Lesson learnt	Recommendation for anticipated definitive trial
Signal of efficacy	The between-group effect size of mean peak plantar pressure reduction indicates that the optimised insole intervention shows promise at 6-months	• The clinical and cost-effectiveness of the optimised insole as part of a large-scale definitive trial is required • Use MPPP as the primary outcome
	Concerns over the durability of the optimised insole	• Consider replacing insoles when MPPP is equal or greater than baseline • Consider measuring MPPP without insole throughout the study period
Delivering the insole intervention	The delivery of the insole intervention was generally acceptable in terms of scientific design principles, although the benefit of the Pulman-house shoe is uncertain	• Continue with existing RCT study design
	Majority of protocol deviations were associated with clinical and operational constraints	• Arrange a stock of house-shoes at each site • Increase capacity of NHS staff to undertake research appointments, which will require negotiation of capability and capacity with individual sites.
	General safety concerns on the Pulman-house shoes were raised from podiatrists, several participants and adverse event data	• Source alternative house-shoe to complement Pulman-house shoe, the provision of which is dependent on clinical judgement
	Significant challenges were encountered with technological infrastructure, the most notable being the conflict with NHS systems	• Include IT support during the set-up and delivery of the study procedures

Table 8.1 Recommendation from developing and testing the intervention (continued)

	Podiatrists struggled with the time taken to deliver the INSTEP programme, especially during the first face-to-face appointment and for administration tasks outside of scheduled appointments.	• The time (and therefore costs) allocated for delivery of the insole intervention (in its current format) should be increased to 1.25 hours, and administration time of 1.0 per week included for podiatrists
Variation and fidelity in the delivery of the insole	The fidelity assessment was appropriate in its coverage and was feasible to implement. The training package to deliver the insole intervention was acceptable, but improvements were suggested by the podiatrists	• Introduce independent fidelity assessments • Include an online webinar for theory base training, to enable the inclusion of a scenario-based exercise for the training session. This will need to be factored into revised estimates of costs associated with delivery of the INSTEP study • Deliver the training package within one month of study opening commencement • Consider pre-existing skill levels of clinicians in manufacturing and providing insoles (to include band 5 clinicians)
Support	Participants reported the supportive influence of podiatrists, family and friends on their behaviour during the study. Podiatrists reported the importance of a support network during the delivery of the study	• Ensure participant information sheet contains a section relevant for family and friends • Promote the importance to podiatrists of supporting participants during the study • Implement a structured support-network for the podiatrists to access, such as WhatsApp social media.

RCT-randomised controlled trial, NHS-National Health Service

8.1.1.2 Recommendations: Study procedures

The recommendations from the study procedures focussed on lessons from participant recruitment, retention and completion rates; suitability and feasibility of eligibility criteria; randomisation; blinding and adherence, all of which were pre-defined objectives of the study (Table 8.2). Challenges were experienced in a number of areas, and lessons were learnt. The recommendations are designed to improve the operationalisation of a future definitive trial and should be relatively straightforward to implement.

Recruitment and retention of participants were lower than anticipated in the fRCT. Therefore, it will be important to utilise those strategies that were successful to augment recruitment. The measures that demonstrated to be most effective in the fRCT sites which recruited to target included personal invites by the podiatry team and active engagement and support by podiatry team members.

Reducing the recruitment target rate to 1-2 participants per month per site would seem realistic for a larger trial, and has been adjusted to allow for operational delays and seasonal variations experienced in the fRCT. Study sites will be encouraged to provide a more flexible approach to locations and times to deliver the research appointments.

To reduce attrition, ensuring a positive relationship between the participant and podiatrist to enable a personalised approach is recommended. Strategies will include the use of reminder letters for appointments and a greater degree of flexibility in the clinical location to deliver the research assessments in

community-based health care establishments, and more available time slots for participants to attend.

Eligibility criteria were pragmatic and easy to apply and can be used in a future RCT, with the stratified randomisation generating homogenous intervention groups. However, strategies for the recruitment of participants of mixed ethnicities and gender that better represents the general population with diabetes and the risk of DFU are recommended. For example, providing patient information leaflets in a range of languages, translating technical phrases and involving a culturally competent person would be relevant strategies.

The use of an active control insole proved effective, by successfully achieving optimal blinding and standardised delivery of the active control across sites. However, using an active control insole requires consideration of whether to include an additional treatment arm in a future RCT where the allocated participants would receive usual care only. Although this would satisfy a true evaluation of the optimised insole against usual care, it would significantly increase the study complexity, sample size, and costs. The use of the sensor to objectively measure adherence to wearing the insole was successful, although a more comprehensive evaluation of variations to the wear time in the house-shoe and insole and wearing other footwear throughout the study duration should be attempted.

As a final suggestion in this section, the importance of disseminating results to both patient participants and podiatrists was prominent, with face-to-face dissemination of results in addition to lay summaries recommended by those participating in the study. Additionally, as part of the MRC implementation

framework, a plan to facilitate adopting the findings of the future RCT into clinical pathways is required.

Table 8.2 Recommendation from study procedures

Activity	Lesson learnt	Recommendation for anticipated definitive trial
Recruitment	Recruitment was highest when a personal approach from podiatry team members was used.	• Recruitment methods should prioritise the personal approach by podiatry team members to optimise recruitment rate, emphasise the importance of positive participant and podiatrist interactions during the study • CI / Trial co-ordinator to engage with podiatry team members to raise study awareness activities and increase their confidence to identify and approach patients,
	Recruitment rate target did not consider operational constraints and seasonal attendance fluctuations	• Set recruitment target of 1-2 participants per site/month
	Limitations of appointment times and locations were given as reasons for non-participation and posed as burdensome for some participants	• Offer option of a morning or afternoon appointment at different clinic locations for participants to reduce burden
	Lack of representation from ethnic and female populations was identified, limiting generalisability to wider population	• Recruit a Black, Asian and Minority ethnic representative and a female patient and public representative to be part of the trial management group
	Some of the participants felt that the patient information sheet was too long, some expressed uncertainty with their understanding of the randomisation process	• The participant information sheets should be fine-tuned to make them more succinct whilst also improving the explanation of the randomisation process

Table 8.2 Recommendation from study procedures (continued)		
Retention	Retention rates were lower than anticipated	• Ensure positive podiatrist-participant relationship during the study period to reduce attrition • Offer morning and afternoon follow-up appointment times for participants to avoid conflicts with usual activities • Provide telephone call reminders for all appointments to reduce participant attrition
Randomisation	Stratification by site and previous ulcer history by centralised electronic procedure worked well to balance groups at baseline	• Continue with existing stratified randomisation procedure
Adherence	The use of data loggers provided an objective measure of wearing the insole. No strategy was in place to distinguish if participants wore other therapeutic footwear and insole during the study	• Continue with data logger to measure adherence to insole • Explore measurement options to capture use of other therapeutic footwear and insoles • Evaluate wearing patterns
Blinding	Participant blinding to treatment allocation was acceptable Assessor blinding was acceptable	• Continue with active control insole to blind participants to treatment allocation • Continue with assessment of anonymised photographs of foot status
Dissemination	Participants expressed their desire to receive the results of the study	• Provide participants with the opportunity to receive both face-to-face and written feedback as part of the dissemination plan

8.1.1.3 Recommendations: Study outcomes

Data on participant demographics, clinical characteristics and a range of potential primary and secondary outcomes were collected to inform a future definitive trial (Table 8.3). The completion and performance rates of the measures were excellent, clearly meeting our pre-defined progression criteria for a definitive trial. However, standardising the collection of clinical variables and exploring an alternative PROM for physical activity would be valuable.

One aim of this fRCT was to select the primary outcome of the future RCT. The primary outcome should be able to provide evidence directly related to the objective of the study, which should reflect the most patient-important outcome perspective (Thoma & Eaves, 2017). The primary outcome measures considered in this feasibility study were MPPP and incidence of DFU.

Completeness and performance of both the incidence of DFU and MPPP were excellent and clearly met the criteria set for progressing to a definitive trial. However, although both primary outcome measures provided information for analysis, MPPP enabled an inference of the signal of efficacy for the optimised insole group compared to the active control insole group.

Nevertheless, MPPP is only considered a surrogate measure of DFU, although it is widely used in studies to evaluate the effectiveness of footwear and insole interventions in people with DM. The systematic review undertaken as part of this PhD research identified that 72% of studies used kinetic outcomes, such as MPPP, as the primary outcome measure when evaluating the therapeutic footwear and insole intervention for people with DPN at risk of DFU (Collings *et al.*, 2020). This contrasted with the incidence of DFU and foot lesions being

used in only 20% of studies with a variety of different measurement techniques. Surrogate measures infer a causal link to the desired patient-relevant outcomes (Heneghan, Goldacre & Mahtani, 2017). They are successfully used when there is a strong link with the desired outcome of interest, although over-interpretation can result in unsuitable interpretations and conclusions (D'Agostino, 2000).

Resultantly, in the absence of recommended core outcome measures for studies for DFU prevention, the conclusion drawn on the basis of this fRCT is that the primary outcome measure for a future trial would be MPPP. However, incidence of DFU and number of diabetic foot ulcer -free days would be valuable secondary outcomes measures, which are particularly helpful if they lend support to the primary endpoint (Vetter & Mascha, 2017). However, any effect-size would be need to be interpreted with caution in terms of their clinical relevance, especially within a six-month study duration. A shorter study duration may create a Type 1 error, although it may be balanced by reduced study costs and participant burden.

The MPPP confidence intervals derived from the fRCT and an allowance of 30% for drop-out, it is estimated that the multi-centre trial would require 265 participants to provide 90% power at the 5% (two-sided) significance level. This would give a definitive indication of clinical effectiveness and allow a small-to-moderate effect size to be detected between the optimised insole compared to the active control insole.

Table 8.3 Recommendations from study outcomes

Activity	Lesson learnt	Recommendation for anticipated definitive trial
Collection and performance of outcome data	Prompts from PenCTU were successful in ensuring only one incomplete data set from baseline data	• Continue with Clinical Trials Unit involvement in future trial • Continue with co-ordinating centre prompting sites for missing baseline data
Completeness and performance of potential primary outcome measures: (mean peak plantar pressure and diabetic foot ulceration)	Both of the potential primary outcome measures had excellent rates of completion at all-time points, were acceptable to participants and produced outcomes that were comparable with those of other similar studies. Criterion for progression to definitive trial was clearly met. However, foot ulceration data originated from safety event data and not blind assessment due to participants withdrawal from study for treatment, thereby introducing possible bias	• The primary outcome for a definitive trial should be mean peak plantar pressure • Incidence of foot ulceration and number of ulcer-free days should be secondary outcomes

Table 8.3 Recommendations from study outcomes (continued)

Completeness and performance of patient reported outcome measures: Nottingham Footcare Questionnaire and International Physical Activity Questionnaire	Both of the potential secondary outcome measures had excellent rates of completion at all-time points. Criterion for progression to definitive trial was clearly met. Participants found the International Physical Activity Questionnaire not specific enough to reflect their needs.	• Further exploration of an alternative measure of physical activity appropriate for people with DPN is required for use in the definitive trial
Sample size calculation	Sample size has been calculated to detect a between-group difference for the primary outcome of mean peak plantar pressure at the primary end point of 6 months post- randomisation.	• Based on the data from this feasibility trial, the estimated sample size for a definitive trial would be 265 participants

In summary, the experience in this fRCT has identified issues and recommendations that will inform the protocol for an anticipated definitive RCT. However, some require further developmental work prior to the definitive trial. It is notable that many of the issues are common to studies involving people with DM. The experience of undertaking this fRCT has provided invaluable learning, which moves one step closer to addressing these very complex issues.

8.2 Implications for clinical practice

This thesis has demonstrated that there is potential for an optimised insole intervention to be introduced into clinical practice for reducing the risk of DFU in people with DPN. However, as this was a fRCT, further evaluation of the clinical and cost-effectiveness of the optimised insole is required, before implementation into practice can be considered. Clinical and cost-effectiveness data will contribute to the body of evidence for using therapeutic footwear and insoles to reducing the risk of DFU. At a local level in the NHS, it will help providers create business cases that demonstrate return on investment, alongside risk/benefit evaluation for patients and organisations.

This study highlighted that there was a decline in the reduction of MPPP in both intervention groups over the six-month timeline of the study, although it is unclear if this is reflective of a decline in insole effectiveness or an increase in diabetic foot pressures. The clinical reduction in MPPP suggests that insoles made from similar materials and which are commonly used in existing practice should be reviewed more frequently, alongside measuring MPPP without the insole. This will ensure their efficacy in reducing risk of DFU is reviewed more

frequently to determine whether they remain fit for purpose or require replacement.

Similarly, the Pulman-house shoe should be prescribed and reviewed more frequently. In this fRCT, some participants reported occasions whereby the house-shoe caused slips and trips in addition to rubs from the velcro fastening. Ensuring that the Pulman-house shoe does not contribute to DFU or other complications, such as falls, is paramount to protect the well-being of patients.

The patient interviews were illuminating in terms of the way that person centred practice could be enhanced when delivering footcare to people with DPN. These included suggestions such as the need for involvement of the whole family, listening to patients with regard to their values and aspiration in relation to their care needs, and investigating the activity level that each individual patient is capable of undertaking, which impacts on DFU risk. Developing a foot-care package that better reflects a patient's physical and psychosocial ability should facilitate an improved standard of care, reflected in reductions of DFU.

One far-reaching implication for clinical practice is the author's development and his dual role as a clinical academic, and as a lead within the NHS podiatry team. Clinical academics are acknowledged for their contribution to quality patient outcomes, not only by virtue of their own research portfolios, but also their leadership that is embedded in clinical practice (Cooper *et al.*, 2019). Leadership is viewed as a key enabler for developing a research culture within an organisation (Slade, Philip & Morris, 2018). Other benefits of clinical academics roles are increased job retention and satisfaction (Wenke *et al.*,

2017) and improved organisation efficiency and collaboration (Harding *et al.*, 2017). However, despite clear benefits of clinical academic roles, barriers to implementation remain, often related to obstacles at board and middle-management levels, although reasons for this inertness are not clearly defined (Carrick-Sen *et al.*, 2019).

Therefore, as a clinical academic, there will be an expectation to overcome these challenges and drive clinically important research questions (Pager, Holden & Golenko, 2012). Embedding a research culture and creating a multi-disciplinary team to deliver clinically relevant and methodologically sound research studies is paramount. Several useful frameworks exist that inform the processes of embedding research into healthcare services (Slade, Philip & Morris, 2018), although efforts to translate, implement and sustain research findings into clinical practice remains a challenge (Byers, 2017).

8.3 Implications for further research

Following the completion of the INSTEP feasibility study, it is important to consider the future direction of its contributions to the body of knowledge and how they will inform research moving forward.

The results and findings from the feasibility study demonstrate that the optimised insole intervention holds promise. Therefore, following the MRC's framework for developing and evaluating complex intervention, the next step would be to design and implement a powered RCT to evaluate the clinical and cost-effectiveness of the optimised insole intervention. The development of the RCT will be informed by INSTEP's fRCT results and recommendations. The

resultant clinical and cost-effectiveness data generated is a vital step in the long-term implementation of the optimised insole intervention. The results of the RCT would be of benefit to public health and therefore a potential funding source would be through the NIHR awards programme. This has the advantage of providing access to an established Clinical Research Network that helps deliver successful trials to fruition.

On the basis of the findings from this fRCT, it is apparent that further exploration of a patient reported outcome measure on activity appropriate for people with DPN is required. The results and findings from the fRCT demonstrate that the existing activity PROM was not suitable for this population. Consequently, exploring PROM's that consider the variation in activity for people with DPN, and especially those with a history of DFU, is required.

On a similar theme, the development of a standardised guideline for reporting foot deformity and ROM would be beneficial to future studies involving people with DPN. A search of the literature highlighted that there is no such standardised reporting list to evaluate the apparent contribution of foot deformity and ROM to DFU.

Other areas of interest implicit from this research, would be to explore participants understanding of therapeutic footwear and insoles use when at home. This information would inform the design of a house-shoe that is acceptable for use, whilst retaining the benefits of protecting and potentially reducing the risk of DFU. Completing a deeper exploration and statistical evaluation of temporal gait patterns to inform the insole design and modification would be also beneficial. This research has also identified questions associated

with the optimal insole material for reducing MPPP and reducing the risk of DFU. As part of the BEUP team, collaborative links with an international counterpart group have been developed to further explore this concept.

8.4 Conclusion - final thoughts

An optimised insole intervention has been developed which aims to reduce the risk of DFU in people with DPN. The results of the feasibility study suggest that the optimised insole holds promise as an intervention, and that a fully powered RCT to evaluate the clinical and cost effectiveness of this intervention is feasible and warranted.

Throughout this PhD programme, the research has contributed to the body of knowledge by synthesising and drawing together the existing evidence of therapeutic footwear and insoles to reduce the risk of DFU in people with DPN. A novel concept of optimising insoles using temporal data and pressure analysis has been presented. The PhD programme has also allowed the acquirement of skills that will enable me to pursue my clinical academic career journey. Subsequently, the next step of the journey will be to undertake the full-scale RCT based on the findings from this fRCT.

This PhD journey has fortunately not been greatly affected by the COVID-19 pandemic. Data collection was completed prior to the outbreak, although the dissemination of results to participants and podiatrists by face-to-face workshops has been postponed until such time as safe meetings can be held. The opportunity to develop new skills based on COVID-19 safe procedures, such as remote informed consent taking, was embraced which will inform the development of the future RCT.

The journey described in this thesis has been most enjoyable and I look forward to developing my skills further and undertaking needed research activities. At a time when healthcare must change to meet the increasing numbers and complications arising from diabetes, developing and testing innovative strategies is essential. The optimised insole is a potentially important strategy for reducing the risk of DFU and reducing the lower-limb burden associated with DPN.

References

Abbott, C. A., Carrington, A. L., Ashe, H., Bath, S., Every, L. C., Griffiths, J., Hann, A. W., Hussein, A., Jackson, N., Johnson, K. E., Ryder, C. H., Torkington, R., Van Ross, E. R., Whalley, A. M., Widdows, P., Williamson, S. & Boulton, A. J. (2002) 'The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort'. *Diabetic Medicine*, 19 (5), pp. 377-384.

Abbott, C. A., Chatwin, K. E., Foden, P., Hasan, A. N., Sange, C., Rajbhandari, S. M., Reddy, P. N., Vileikyte, L., Bowling, F. L. & Boulton, A. J. (2019) 'Innovative intelligent insole system reduces diabetic foot ulcer recurrence at plantar sites: a prospective, randomised, proof-of-concept study'. *The Lancet Digital Health*, 1 (6), pp. e308-e318.

Abouaesha, F., van Schie, C. H. M., Griffths, G. D., Young, R. J. & Boulton, A. J. M. (2001) 'Plantar Tissue Thickness Is Related to Peak Plantar Pressure in the High-Risk Diabetic Foot'. *Diabetes Care*, 24 (7), pp. 1270-1274.

Ahroni, J. H., Boyko, E. J. & Forsberg, R. (1998) 'Reliability of F-Scan in-shoe measurements of plantar pressure'. *Foot & Ankle International*, 19 (10), pp. 668-673.

Ahuja, A. S. (2019) 'Should RCT's be used as the gold standard for evidence based medicine?'. *Integrative Medicine Research*, 8 (1), pp. 31-32.

Akturk, A., van Netten, J. J., Scheer, R., Vermeer, M. & van Baal, J. G. (2019) 'Ulcer-free survival days and ulcer healing in patients with diabetic foot ulcers: A prospective cohort study'. *International Wound Journal*, 16 (6), pp. 1365-1372.

Alam, U., Azmi, S., Malik, R. A., Jugdey, R. S., Riley, D. R., Rajbhandari, S. & D'Aout, K. (2017) 'Diabetic Neuropathy and Gait: A Review'. *Diabetes Therapy*, 8 (6), pp. 1253-1264.

Albert, S. & Rinoie, C. (1994) 'Effect of custom orthotics on plantar pressure distribution in the pronated diabetic foot'. *Journal of Foot & Ankle Surgery*, 33 (6), pp. 598-604.

Altman, D. G. & Bland, J. M. (1999) 'Statistics notes. Treatment allocation in controlled trials: why randomise?'. *British Medical Journal*, 318 (7192), pp. 1209-1209.

An, M., Dusing, S. C., Harbourne, R. T., Sheridan, S. M. & Consortium, S.-P. (2020) 'What Really Works in Intervention? Using Fidelity Measures to Support Optimal Outcomes'. *Physical therapy*, 100 (5), pp. 757-765.

Andersen, H., Gjerstad, M. D. & Jakobsen, J. (2004) 'Atrophy of foot muscles: a measure of diabetic neuropathy'. *Diabetes Care*, 27 (10), pp. 2382-2385.

Anderson, C. (2010) 'Presenting and evaluating qualitative research'. *American journal of pharmaceutical education*, 74 (8), p. 141 DOI: doi.org/10.5688/aj7408141.

Ansari, S., Panhwar, A. H. & Mahesar, G. A. (2016) 'Mixed Methods Research: Ontological, Epistemological and Methodological underpinnings'. *ARIEL-An International Research Journal of English Language and Literature*, 27 pp. 133-141.

Arain, M., Campbell, M. J., Cooper, C. L. & Lancaster, G. A. (2010) 'What is a pilot or feasibility study? A review of current practice and editorial policy'. *BMC Medical Research Methodology*, 10 (1), pp. 1-7.

Armstrong, D. G., Boulton, A. J. M. & Bus, S. A. (2017) 'Diabetic Foot Ulcers and Their Recurrence'. *New England Journal of Medicine*, 376 (24), pp. 2367-2375.

Armstrong, D. G., Cohen, K., Courric, S., Bharara, M. & Marston, W. (2011) 'Diabetic foot ulcers and vascular insufficiency: our population has changed, but our methods have not'. *Journal of Diabetes Science and Technology*, 5 (6), pp. 1591-1595.

Armstrong, D. G., Kanda, V. A., Lavery, L. A., Marston, W., Mills, J. L. & Boulton, A. J. (2013) 'Mind the gap: disparity between research funding and costs of care for diabetic foot ulcers'. *Diabetes Care*, 36 (7), pp. 1815-1817.

Armstrong, D. G., Lavery, L. A. & Harkless, L. B. (1998) 'Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation'. *Diabetes Care*, 21 (5), pp. 855-859.

Armstrong, D. G., Peters, E. J., Athanasiou, K. A. & Lavery, L. A. (1998) 'Is there a critical level of plantar foot pressure to identify patients at risk for neuropathic foot ulceration?'. *Journal of Foot & Ankle Surgery*, 37 (4), pp. 303-307.

Armstrong, D. G., Stacpoole-Shea, S., Nguyen, H. & Harkless, L. B. (1999) 'Lengthening of the Achilles tendon in diabetic patients who are at high risk for ulceration of the foot'. *Journal of Bone & Joint Surgery, American Volume*, 81 (4), pp. 535-538.

Arosi, I., Hiner, G. & Rajbhandari, S. (2016) 'Pathogenesis and Treatment of Callus in the Diabetic Foot'. *Current diabetes reviews*, 12 (3), pp. 179-183.

Arts, M. L., de Haart, M., Bus, S. A., Bakker, J. P., Hacking, H. G. & Nollet, F. (2014) 'Perceived usability and use of custom-made footwear in diabetic

patients at high risk for foot ulceration'. *Journal of Rehabilitation Medicine (Stiftelsen Rehabiliteringsinformation)*, 46 (4), pp. 357-362.

Arts, M. L. J. & Bus, S. A. (2011) 'Twelve steps per foot are recommended for valid and reliable in-shoe plantar pressure data in neuropathic diabetic patients wearing custom made footwear'. *Clinical Biomechanics*, 26 (8), pp. 880-884.

Arts, M. L. J., Haart, M., Waaijman, R., Dahmen, R., Berendsen, H., Nollet, F. & Bus, S. A. (2015) 'Data-driven directions for effective footwear provision for the high-risk diabetic foot'. *Diabetic Medicine*, 32 (6), pp. 790-797.

Arts, M. L. J., Waaijman, R., de Haart, M., Keukenkamp, R., Nollet, F. & Bus, S. A. (2012) 'Offloading effect of therapeutic footwear in patients with diabetic neuropathy at high risk for plantar foot ulceration'. *Diabetic Medicine*, 29 (12), pp. 1534-1541.

Atkinson, G. & Nevill, A. M. (1998) 'Statistical Methods For Assessing Measurement Error (Reliability) in Variables Relevant to Sports Medicine'. *Sports Medicine*, 26 (4), pp. 217-238.

Avery, K. N. L., Williamson, P. R., Gamble, C., O'Connell Francischetto, E., Metcalfe, C., Davidson, P., Williams, H. & Blazeby, J. M. (2017) 'Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies'. *BMJ Open*, 7 (2), pp. e013537.

Bacarin, T. A., Sacco, I. C. N. & Hennig, E. M. (2009) 'Plantar pressure distribution patterns during gait in diabetic neuropathy patients with a history of foot ulcers'. *Clinics*, 64 pp. 113-120.

Bader, D. L. & Worsley, P. R. (2018) 'Technologies to monitor the health of loaded skin tissues'. *BioMedical Engineering OnLine*, 17 (1), p. 40 DOI: 10.1186/s12938-018-0470-z (Accessed: Apr 12).

Bang, H., Ni, L. & Davis, C. E. (2004) 'Assessment of blinding in clinical trials'. *Controlled Clinical Trials*, 25 (2), pp. 143-156.

Barn, R., Waaijman, R., Nollet, F., Woodburn, J. & Bus, S. A. (2015) 'Predictors of Barefoot Plantar Pressure during Walking in Patients with Diabetes, Peripheral Neuropathy and a History of Ulceration'. *PLoS One*, 10 (2), p. e0117443 DOI: 10.1371/journal. pone.011744.

Barnett, S. (2002) 'The clinical effectiveness of orthoses prescribed to control and reduce diabetic foot pathology'. *University of the West of England at Bristol (United Kingdom)*. [thesis]. Available at: http://hdl.handle.net/10068/598967

Bauman, A., Ainsworth, B. E., Bull, F., Craig, C. L., Hagströmer, M., Sallis, J. F., Pratt, M. & Sjöström, M. (2009) 'Progress and pitfalls in the use of the

International Physical Activity Questionnaire (IPAQ) for adult physical activity surveillance'. *Journal of Physical Activity and Health*, 6 (s1), pp. S5-S8.

Beidas, R. S., Cross, W. & Dorsey, S. (2014) 'Show me, don't tell me: Behavioral rehearsal as a training and analogue fidelity tool'. *Cognitive and Behavioral Practice*, 21 (1), pp. 1-11.

Bellg, A. J., Borrelli, B., Resnick, B., Hecht, J., Minicucci, D. S., Ory, M., Ogedegbe, G., Orwig, D., Ernst, D. & Czajkowski, S. (2004) 'Enhancing treatment fidelity in health behavior change studies: best practices and recommendations from the NIH Behavior Change Consortium'. *Health Psychology*, 23 (5), pp. 443-451.

Bennell, K., Talbot, R., Wajswelner, H., Techovanich, W., Kelly, D. & Hall, A. J. (1998) 'Intra-rater and inter-rater reliability of a weight-bearing lunge measure of ankle dorsiflexion'. *Australian Journal of Physiotherapy*, 44 (3), pp. 175-180.

Berger, R. (2015) 'Now I see it, now I don't: Researcher's position and reflexivity in qualitative research'. *Qualitative Research*, 15 (2), pp. 219-234.

Birke, J. A., Foto, J. G. & Pfiefer, L. A. (1999) 'Effect of orthosis material hardness on walking pressure in high-risk diabetes patients'. *Journal of Prosthetics & Orthotics (JPO)*, 11 (2), pp. 43-46.

Blanche, E. I., Fogelberg, D., Diaz, J., Carlson, M. & Clark, F. (2011) 'Manualization of occupational therapy interventions: illustrations from the pressure ulcer prevention research program'. *The American journal of occupational therapy : official publication of the American Occupational Therapy Association*, 65 (6), pp. 711-719.

Bland, J. M. & Altman, D. G. (1999) 'Measuring agreement in method comparison studies'. *Statistical methods in medical research*, 8 (2), pp. 135-160.

Blatch-Jones, A. J., Pek, W., Kirkpatrick, E. & Ashton-Key, M. (2018) 'Role of feasibility and pilot studies in randomised controlled trials: a cross-sectional study'. *BMJ Open*, 8 (9), p. e022233 DOI: 10.1136/bmjopen-2018-022233 [Online]. Available at: https://bmjopen.bmj.com/content/bmjopen/8/9/e022233.full.pdf.

Bleijenberg, N., de Man-van Ginkel, J. M., Trappenburg, J. C. A., Ettema, R. G. A., Sino, C. G., Heim, N., Hafsteindóttir, T. B., Richards, D. A. & Schuurmans, M. J. (2018) 'Increasing value and reducing waste by optimizing the development of complex interventions: Enriching the development phase of the Medical Research Council (MRC) Framework'. *International Journal of Nursing Studies*, 79 pp. 86-93.

Bluestone, J., Johnson, P., Fullerton, J., Carr, C., Alderman, J. & BonTempo, J. (2013) 'Effective in-service training design and delivery: evidence from an integrative literature review'. *Human Resources for Health*, 11 (1), p. 51 DOI: 10.1186/1478-4491-11-51 [Online]. Available at: https://doi.org/10.1186/1478-4491-11-51 (Accessed: 2013/10/01).

Bonanno, D. R., Landorf, K. B., Murley, G. S. & Menz, H. B. (2015) 'Selecting control interventions for use in orthotic trials: the methodological benefits of sham orthoses'. *Contemporary Clinical Trials*, 42 p. 257 DOI: 10.1016/j.cct.2015.05.008.

Bonner, T., Foster, M. & Spears-Lanoix, E. (2016) 'Type 2 diabetes-related foot care knowledge and foot self-care practice interventions in the United States: a systematic review of the literature'. *Diabetic Foot and Ankle*, 7 p. 29758 DOI: 10.3402/dfa.v7.29758.

Booth, M. (2000) 'Assessment of Physical Activity: An International Perspective'. *Research Quarterly For Exercise And Sport*, 71 (sup2), pp. 114-120.

Bornhöft, G., Maxion-Bergemann, S., Wolf, U., Kienle, G. S., Michalsen, A., Vollmar, H. C., Gilbertson, S. & Matthiessen, P. F. (2006) 'Checklist for the qualitative evaluation of clinical studies with particular focus on external validity and model validity'. *BMC Medical Research Methodology*, 6 (1), p. 56 DOI:

10.1186/1471-2288-6-56 [Online]. Available at: https://doi.org/10.1186/1471-2288-6-56 (Accessed: 2006/12/11).

Boulton, A. J. (1998) 'Guidelines for diagnosis and outpatient management of diabetic peripheral neuropathy. European Association for the Study of Diabetes, Neurodiab'. *Diabetes & Metabolism*, 24 Suppl 3 pp. 55-65.

Boulton, A. J. (2006) 'The diabetic foot'. *Medicine*, 34 (3), pp. 87-90.

Boulton, A. J. (2010) 'What you can't feel can hurt you'. *Journal of vascular surgery*, 52 (3 Suppl), pp. 28s-30s.

Boulton, A. J. (2020) 'The Pathway to Ulceration: Aetiopathogenesis and Screening'. *The Foot in Diabetes*, pp. 105-123.

Boulton, A. J. M. (2013) 'The pathway to foot ulceration in diabetes'. *Medical Clinics of North America*, 97 (5), pp. 775-790.

Boulton, A. J. M. (2019) 'The diabetic foot'. *Medicine (United Kingdom)*, 47 (2), pp. 100-105.

Boulton, A. J. M., Armstrong, D. G., Albert, S. F., Frykberg, R. G., Hellman, R., Kirkman, M. S., Lavery, L. A., LeMaster, J. W., Mills, J. L., Mueller, M. J.,

Sheehan, P. & Wukich, D. K. (2008) 'Comprehensive Foot Examination and Risk Assessment'. *A report of the Task Force of the Foot Care Interest Group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists*, 31 (8), pp. 1679-1685.

Boulton, A. J. M., Hardisty, C. A., Betts, R. P., Franks, C. I., Worth, R. C., Ward, J. D. & Duckworth, T. (1983) 'Dynamic Foot Pressure and Other Studies as Diagnostic and Management Aids in Diabetic Neuropathy'. *Diabetes Care*, 6 (1), pp. 26-33.

Boutron, I., Altman, D. G., Moher, D., Schulz, K. F. & Ravaud, P. (2017) 'CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts'. *Annals Of Medicine*, 167 (1), pp. 40-47.

Boutron, I., Guittet, L., Estellat, C., Moher, D., Hróbjartsson, A. & Ravaud, P. (2007) 'Reporting Methods of Blinding in Randomized Trials Assessing Nonpharmacological Treatments'. *PLoS Medicine*, 4 (2), p. e61 DOI: 10.1371/journal.pmed.0040061 [Online]. Available at: https://doi.org/10.1371/journal.pmed.0040061.

Boyer, K. A., Johnson, R. T., Banks, J. J., Jewell, C. & Hafer, J. F. (2017) 'Systematic review and meta-analysis of gait mechanics in young and older adults'. *Experimental Gerontology*, 95 pp. 63-70.

Boyko, E. J., Ahroni, J. H., Stensel, V., Forsberg, R. C., Davignon, D. R. & Smith, D. G. (1999) 'A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study'. *Diabetes Care*, 22 (7), pp. 1036-1042.

Braun, V. & Clarke, V. (2006) 'Using thematic analysis in psychology'. *Qualitative Research in Psychology*, 3 (2), pp. 77-101.

Braun, V. & Clarke, V. (2020) 'One size fits all? What counts as quality practice in (reflexive) thematic analysis?'. *Qualitative Research in Psychology*, pp. 1-25.

Brewster, S., Bartholomew, J., Holt, R. & Price, H. (2020) 'Non-attendance at diabetes outpatient appointments: a systematic review'. *Diabetic Medicine*, 37 (9), pp. 1427-1442.

Broglio, K. (2018) 'Randomization in Clinical Trials: Permuted Blocks and Stratification'. *JAMA*, 319 (21), pp. 2223-2224.

Brown, B. B., Patel, C., McInnes, E., Mays, N., Young, J. & Haines, M. (2016) 'The effectiveness of clinical networks in improving quality of care and patient outcomes: a systematic review of quantitative and qualitative studies'. *BMC Health Services Research*, 16 (1), pp. 360-360.

Brown, M. J., Chuang-Stein, C. & Kirby, S. (2012) 'Designing Studies to Find Early Signals of Efficacy'. *Journal Of Biopharmaceutical Statistics*, 22 (6), pp. 1097-1108.

Brown, S., Thorpe, H., Hawkins, K. & Brown, J. (2005) 'Minimization—reducing predictability for multi-centre trials whilst retaining balance within centre'. *Statistics in Medicine*, 24 (24), pp. 3715-3727.

Buldt, A. K., Allan, J. J., Landorf, K. B. & Menz, H. B. (2018) 'The relationship between foot posture and plantar pressure during walking in adults: A systematic review'. *Gait Posture*, 62 pp. 56-67.

Burnfield, J. M., Few, C. D., Mohamed, O. S. & Perry, J. (2004) 'The influence of walking speed and footwear on plantar pressures in older adults'. *Clinical Biomechanics*, 19 (1), pp. 78-84.

Burns, J., Wegener, C., Begg, L., Vicaretti, M. & Fletcher, J. (2009) 'Randomized trial of custom orthoses and footwear on foot pain and plantar pressure in diabetic peripheral arterial disease'. *Diabetic Medicine*, 26 (9), pp. 893-899.

Bus, S., Valk, G., Van Deursen, R., Armstrong, D., Caravaggi, C., Hlaváček, P., Bakker, K. & Cavanagh, P. (2008) 'The effectiveness of footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in

diabetes: a systematic review'. *Diabetes/metabolism research and reviews*, 24 (S1), pp. S162-S180.

Bus, S. A., Deursen, R. W., Armstrong, D. G., Lewis, J. E. A., Caravaggi, C. F., Cavanagh, P. R. & van Deursen, R. W. (2016) 'Footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in patients with diabetes: a systematic review'. *Diabetes/Metabolism Research & Reviews*, 32 pp. 99-118.

Bus, S. A., Haspels, R. & Busch-Westbroek, T. E. (2011) 'Evaluation and optimization of therapeutic footwear for neuropathic diabetic foot patients using in-shoe plantar pressure analysis'. *Diabetes Care*, 34 (7), pp. 1595-1600.

Bus, S. A., Lavery, L. A., Monteiro-Soares, M., Rasmussen, A., Raspovic, A., Sacco, I. C. & van Netten, J. J. (2020) 'Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2019 update)'. *Diabetes/metabolism research and reviews*, 36 p. e3269 DOI: 10.1002/dmrr.3269.

Bus, S. A., Maas, M., de Lange, A., Michels, R. P. & Levi, M. (2005) 'Elevated plantar pressures in neuropathic diabetic patients with claw/hammer toe deformity'. *Journal of Biomechanics*, 38 (9), pp. 1918-1925.

Bus, S. A., Ulbrecht, J. S. & Cavanagh, P. R. (2004) 'Pressure relief and load redistribution by custom-made insoles in diabetic patients with neuropathy and foot deformity'. *Clinical Biomechanics*, 19 (6), pp. 629-638.

Bus, S. A. & van Netten, J. J. (2016) 'A shift in priority in diabetic foot care and research: 75% of foot ulcers are preventable'. *Diabetes/Metabolism Research & Reviews*, 32 pp. 195-200.

Bus, S. A., Waaijman, R., Arts, M., Haart, M. D., Busch-Westbroek, T., Van Baal, J. & Nollet, F. (2013) 'Effect of custom-made footwear on foot ulcer recurrence in diabetes: A multicenter randomized controlled trial'. *Diabetes Care*, 36 (12), pp. 4109-4116.

Bus, S. A., Waaijman, R. & Nollet, F. (2012) 'New monitoring technology to objectively assess adherence to prescribed footwear and assistive devices during ambulatory activity'. *Archives of Physical Medicine & Rehabilitation*, 93 (11), pp. 2075-2079.

Bus, S. A., Yang, Q. X., Wang, J. H., Smith, M. B., Wunderlich, R. & Cavanagh, P. R. (2002) 'Intrinsic muscle atrophy and toe deformity in the diabetic neuropathic foot: a magnetic resonance imaging study'. *Diabetes Care*, 25 (8), pp. 1444-1450.

Busch, K. & Chantelau, E. (2003) 'Effectiveness of a new brand of stock ‘diabetic’shoes to protect against diabetic foot ulcer relapse. A prospective cohort study'. *Diabetic Medicine*, 20 (8), pp. 665-669.

Byers, V. (2017) 'The challenges of leading change in health-care delivery from the front-line'. *Journal of Nursing Management*, 25 (6), pp. 449-456.

Callaghan, B. C., Little, A. A., Feldman, E. L. & Hughes, R. A. C. (2012) 'Enhanced glucose control for preventing and treating diabetic neuropathy'. *Cochrane Database of Systematic Reviews*, 10.1002/14651858(6), DOI: 10.1002/14651858.

Calvert, M., Blazeby, J., Altman, D. G., Revicki, D. A., Moher, D. & Brundage, M. D. (2013) 'Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension'. *The Journal of the American Medical Association*, 309 (8), pp. 814-822.

Campbell, M., Fitzpatrick, R., Haines, A., Kinmonth, A. L., Sandercock, P., Spiegelhalter, D. & Tyrer, P. (2000) 'Framework for design and evaluation of complex interventions to improve health'. *British Medical Journal*, 321 (7262), pp. 694-696.

Carinci, F., Uccioli, L., Massi Benedetti, M. & Klazinga, N. S. (2020) 'An in-depth assessment of diabetes-related lower extremity amputation rates 2000–2013

delivered by twenty-one countries for the data collection 2015 of the Organization for Economic Cooperation and Development (OECD)'. *Acta Diabetologica*, 57 (3), pp. 347-357.

Carrick-Sen, D. M., Moore, A., Davidson, P., Gendong, H. & Jackson, D. (2019) 'International perspectives of nurses, midwives and allied health professionals clinical academic roles: Are we at tipping point?'. *International Journal of Practice-based Learning in Health and Social Care*, 7 (2), pp. 1-15.

Castleberry, A. & Nolen, A. (2018) 'Thematic analysis of qualitative research data: Is it as easy as it sounds?'. *Currents in Pharmacy Teaching and Learning*, 10 (6), pp. 807-815.

Catalfamo, P., Moser, D., Ghoussayni, S. & Ewins, D. (2008) 'Detection of gait events using an F-Scan in-shoe pressure measurement system'. *Gait Posture*, 28 (3), pp. 420-426.

Cavanagh, P. R. & Bus, S. A. (2010) 'Off-loading the diabetic foot for ulcer prevention and healing'. *Journal of American Podiatric Medical Association*, 100 (5), pp. 360-368.

Cavanagh, P. R., Simoneau, G. G. & Ulbrecht, J. S. (1993) 'Ulceration, unsteadiness, and uncertainty: the biomechanical consequences of diabetes mellitus'. *Journal of Biomechanics*, 26 Supplement 1 pp. 23-40.

Chan, A. W., Tetzlaff, J. M., Altman, D. G., Laupacis, A., Gøtzsche, P. C., Krleža-Jerić, K., Hróbjartsson, A., Mann, H., Dickersin, K., Berlin, J. A., Doré, C. J., Parulekar, W. R., Summerskill, W. S., Groves, T., Schulz, K. F., Sox, H. C., Rockhold, F. W., Rennie, D. & Moher, D. (2013) 'SPIRIT 2013 statement: defining standard protocol items for clinical trials'. *Annals Of Medicine*, 158 (3), pp. 200-207.

Chan, C. B., Ryan, D. A. & Tudor-Locke, C. (2006) 'Relationship between objective measures of physical activity and weather: a longitudinal study'. *International Journal of Behavioral Nutrition and Physical Activity*, 3 (1), pp. 21.

Chantelau, E. & Haage, P. (1994a) 'An audit of cushioned diabetic footwear: relation to patient compliance'. *Diabetic Medicine*, 11 (1), pp. 114-116 113p.

Chantelau, E. & Haage, P. (1994b) 'An audit of cushioned diabetic footwear: relation to patient compliance'. *Diabetic Medicine*, 11 (1), pp. 114-116.

Chantelau, E., Kushner, T. & Spraul, M. (1990) 'How effective is cushioned therapeutic footwear in protecting diabetic feet? A clinical study'. *Diabetic Medicine*, 7 (4), pp. 355-359.

Chapman, G. J., Parkes, M. J., Forsythe, L., Felson, D. & Jones, R. (2015) 'Ankle motion influences the external knee adduction moment and may predict

who will respond to lateral wedge insoles?: an ancillary analysis from the SILK trial'. *Osteoarthritis and Cartilage*, 23 (8), pp. 1316-1322.

Chapman, J. D., Preece, S., Braunstein, B., Höhne, A., Nester, C. J., Brueggemann, P. & Hutchins, S. (2013) 'Effect of rocker shoe design features on forefoot plantar pressures in people with and without diabetes'. *Clinical Biomechanics*, 28 (6), pp. 679-685.

Chapman, L. S., Redmond, A. C., Landorf, K. B., Rome, K., Keenan, A.-M., Waxman, R., Alcacer-Pitarch, B., Siddle, H. J. & Backhouse, M. R. (2018) 'A survey of foot orthoses prescription habits amongst podiatrists in the UK, Australia and New Zealand'. *Journal of foot and ankle research*, 11 (1), p. 64 DOI: 10.1186/s13047-018-0304-z (Accessed: 2018/11/26).

Chen, B. & Bates, B. T. (2000) 'Comparison of F-Scan in-sole and AMTI forceplate system in measuring vertical ground reaction force during gait'. *Physiotherapy Theory And Practice*, 16 (1), pp. 43-53.

Chevalier, T. L., Hodgins, H. & Chockalingam, N. (2010) 'Plantar pressure measurements using an in-shoe system and a pressure platform: A comparison'. *Gait Posture*, 31 (3), pp. 397-399.

Choy, L. T. (2014) 'The strengths and weaknesses of research methodology: Comparison and complimentary between qualitative and quantitative

approaches'. *IOSR Journal of Humanities and Social Science*, 19 (4), pp. 99-104.

Churchman, N. (2008) 'A retrospective audit of footwear use by high-risk individuals in North Derbyshire'. *The Diabetic Foot*, 11 (1), pp. 10-15.

Clarke, V. & Braun, B. (2017) 'The SAGE Handbook of Qualitative Research in Psychology'.[in (pages 17-36) London: SAGE Publications Ltd. 10.4135/9781526405555. Available at: https://methods.sagepub.com/book/the-sage-handbook-of-qualitative-research-in-psychology-second-edition (Accessed:Clarke, V. & Braun, B. 8th September 2020).

Cohn, S., Clinch, M., Bunn, C. & Stronge, P. (2013) 'Entangled complexity: why complex interventions are just not complicated enough'. *Journal of Health Services Research & Policy*, 18 (1), pp. 40-43.

Colagiuri, S., Marsden, L. L., Naidu, V. & Taylor, L. (1995) 'The use of orthotic devices to correct plantar callus in people with diabetes'. *Diabetes Research and Clinical Practice*, 28 (1), pp. 29-34.

Collings, R., Freeman, J., Glasser, S., Paton, J. & Latour, J. M. (2017) 'Footwear and insole design features to prevent foot ulceration in people with diabetes: A systematic review protocol'. *JBI Database of Systematic Reviews and Implementation Reports*, 15 (7), pp. 1824-1834.

Collings, R., Freeman, J., Latour, J. M. & Paton, J. (2020) 'Footwear and insole design features for offloading the diabetic at risk foot—A systematic review and meta-analyses'. *Endocrinology, diabetes & metabolism*, 10.1002/edm2.132p. e00132 DOI: 10.1002/edm2.132 (Accessed: 2020).

Collings, R., Freeman, J. A., Latour, J., Vickery, P. J., Glasser, S., Lepesis, V., Enki, D. & Paton, J. (2019) 'INSoles To Ease Pressure (INSTEP) Study: a multicentre, randomised controlled feasibility study to compare the effectiveness of a novel instant optimised insole with a standard insole for people with diabetic neuropathy: a study protocol'. *BMJ Open*, 9 (3), p. e029185 DOI: 10.1136/bmjopen-2019-029185 (Accessed: Mar 2019).

Cooper, J., Mitchell, K., Richardson, A. & Bramley, L. (2019) 'Developing the Role of the Clinical Academic Nurse, Midwife and Allied Health Professional in Healthcare Organisations'. *International Journal of Practice-based Learning in Health and Social Care*, 7 (2), pp. 16-24.

Correa, V. C., Lugo-Agudelo, L. H., Aguirre-Acevedo, D. C., Contreras, J. A. P., Borrero, A. M. P., Patiño-Lugo, D. F. & Valencia, D. A. C. (2020) 'Individual, health system, and contextual barriers and facilitators for the implementation of clinical practice guidelines: a systematic metareview'. *Health Research Policy and Systems*, 18 (1), p. 74 DOI: 10.1186/s12961-020-00588-8 [Online].

Available at: https://doi.org/10.1186/s12961-020-00588-8 (Accessed: 2020/06/29).

Cowley, M. S., Boyko, E. J., Shofer, J. B., Ahroni, J. H. & Ledoux, W. R. (2008) 'Foot ulcer risk and location in relation to prospective clinical assessment of foot shape and mobility among persons with diabetes'. *Diabetes Research and Clinical Practice*, 82 (2), pp. 226-232.

Craig, C. L., Marshall, A. L., Sjöström, M., Bauman, A. E., Booth, M. L., Ainsworth, B. E., Pratt, M., Ekelund, U., Yngve, A., Sallis, J. F. & Oja, P. (2003) 'International physical activity questionnaire: 12-country reliability and validity'. *Medicine & Science in Sports & Exercise*, 35 (8), pp. 1381-1395.

Craig, P., Di Ruggiero, E., Frolich, K. L., Mykhalovskiy, E., White, M., Campbell, R., Cummins, S., Edwards, N., Hunt, K. & Kee, F. (2018a) *Taking account of context in population health intervention research: guidance for producers, users and funders of research.* Southampton: National Institute for Health Research. Available.

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I. & Petticrew, M. (2008) 'Developing and evaluating complex interventions: the new Medical Research Council guidance'. *British Medical Journal*, 337 p. a1655 DOI: 10.1136/bmj.a1655.

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I. & Petticrew, M. (2013) 'Developing and evaluating complex interventions: the new Medical Research Council guidance'. *International Journal of Nursing Studies*, 50 (5), pp. 587-592.

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I. & Petticrew, M. (2018b) 'Developing and evaluating complex interventions: new guidance.'. [Online]. Available at: https://mrc.ukri.org/documents/pdf/complex-interventions-guidance. (Accessed: 17th August).

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I. & Petticrew, M. (2020) 'Developing and evaluating complex interventions: new guidance'. *Developing and evaluating complex interventions: new guidance. Medical Research Council.* [Online]. Available at: https://mrc.ukri.org/documents/pdf/developing-and-evaluating-complex-interventions/ (Accessed: 17th August).

Crawford, F., Nicolson, D. J., Amanna, A. E., Martin, A., Gupta, S., Leese, G. P., Heggie, R., Chappell, F. M. & McIntosh, H. H. (2020) 'Preventing foot ulceration in diabetes: systematic review and meta-analyses of RCT data'. *Diabetologia*, 63 (1), pp. 49-64.

Cresswell, J. & Plano Clark, V. (2011) *Designing and conducting mixed method research. 2nd Sage.* Thousand Oaks, CA. Sage Publications.

Creswell, J. W. (2014) *A concise introduction to mixed methods research.* Thousand Oaks, CA, USA: SAGE publications.

Creswell, J. W. & Clark, V. L. P. (2017) *Designing and conducting mixed methods research.* Thousand Oaks, CA, USA: Sage publications.

Creswell, J. W. & Poth, C. N. (2016) *Qualitative inquiry and research design: Choosing among five approaches.* Thousand Oaks, CA, USA: Sage publications.

Cronin, N. J., Peltonen, J., Ishikawa, M., Komi, P. V., Avela, J., Sinkjaer, T. & Voigt, M. (2010) 'Achilles tendon length changes during walking in long-term diabetes patients'. *Clinical Biomechanics*, 25 (5), pp. 476-482.

Cumming, A. & Bayliff, T. (2011) 'Plantar pressure: comparing two poron insoles'. *Diabetic Foot Journal*, 14 (2), pp. 86-89.

D'Agostino, R. B., Jr. (2000) 'Debate: The slippery slope of surrogate outcomes'. *Trials*, 1 (2), pp. 76-78.

D'Silva, L. J., Lin, J., Staecker, H., Whitney, S. L. & Kluding, P. M. (2016) 'Impact of Diabetic Complications on Balance and Falls: Contribution of the Vestibular System'. *Physical therapy*, 96 (3), pp. 400-409.

Daly, J., Willis, K., Small, R., Green, J., Welch, N., Kealy, M. & Hughes, E. (2007) 'A hierarchy of evidence for assessing qualitative health research'. *Journal Of Clinical Epidemiology*, 60 (1), pp. 43-49.

Dananberg, H. J. (2000) 'Sagittal plane biomechanics. American Diabetes Association'. *Journal of American Podiatry Association*, 90 (1), pp. 47-50.

Day, S. J. & Altman, D. G. (2000) 'Blinding in clinical trials and other studies'. *British Medical Journal*, 321 (7259), p. 504 DOI: 10.1136/bmj.321.7259.504 [Online]. Available at: https://www.bmj.com/content/bmj/321/7259/504.full.pdf.

Daykin, A., Clement, C., Gamble, C., Kearney, A., Blazeby, J., Clarke, M., Lane, J. A. & Shaw, A. (2018) ''Recruitment, recruitment, recruitment' – the need for more focus on retention: a qualitative study of five trials'. *Trials*, 19 (1), p. 76 DOI: 10.1186/s13063-018-2467-0 [Online]. Available at: https://doi.org/10.1186/s13063-018-2467-0 (Accessed: 2018/01/29).

Deschamps, K., Matricali, G. A., Roosen, P., Desloovere, K., Bruyninckx, H., Spaepen, P., Nobels, F., Tits, J., Flour, M. & Staes, F. (2013) 'Classification of forefoot plantar pressure distribution in persons with diabetes: a novel perspective for the mechanical management of diabetic foot?'. *PLoS One*, 8 (11), p. e79924 DOI: 10.1371/journal.pone.0079924.

Dhatariya, K., Panter, K. & Gooday, C. (2011) 'Patients' perceptions of a shoe-fitting service at a diabetic foot clinic'. *The Diabetic Foot*, 14 (1), pp. 6-47.

Digital, N. (2018) *National Diabetes Foot care Audit Report (NDFA)* https://files.digital.nhs.uk/73/39E604/ndfa-3ar-rep-1.pdf

Dingwell, J. B. & Cavanagh, P. R. (2001) 'Increased variability of continuous overground walking in neuropathic patients is only indirectly related to sensory loss'. *Gait Posture*, 14 (1), pp. 1-10.

Dodgson, J. E. (2019) 'Reflexivity in Qualitative Research'. *Journal of Human Lactation*, 35 (2), pp. 220-222.

Donaghue, V. M., Sarnow, M. R., Giurini, J. M., Chrzan, J. S., Habershaw, G. M. & Veves, A. (1996) 'Longitudinal in-shoe foot pressure relief achieved by specially designed footwear in high risk diabetic patients'. *Diabetes Research and Clinical Practice*, 31 (1), pp. 109-114.

Donald, G. (2018) 'A brief summary of pilot and feasibility studies: Exploring terminology, aims, and methods'. *European Journal of Integrative Medicine*, 24 pp. 65-70.

Dudley, L., Gamble, C., Preston, J., Buck, D., Group, E. P. A., Hanley, B., Williamson, P. & Young, B. (2015) 'What Difference Does Patient and Public

Involvement Make and What Are Its Pathways to Impact? Qualitative Study of Patients and Researchers from a Cohort of Randomised Clinical Trials'. *PLoS One*, 10 (6), pp. e0128817-e0128817 *PubMed* DOI: 10.1371/journal.pone.0128817.

Duley, L., Gillman, A., Duggan, M., Belson, S., Knox, J., McDonald, A., Rawcliffe, C., Simon, J., Sprosen, T., Watson, J. & Wood, W. (2018) 'What are the main inefficiencies in trial conduct: a survey of UKCRC registered clinical trials units in the UK'. *Trials*, 19 (1), p. 15 DOI: 10.1186/s13063-017-2378-5 [Online]. Available at: https://doi.org/10.1186/s13063-017-2378-5 (Accessed: 2018/01/08).

Duncan, E., O'Cathain, A., Rousseau, N., Croot, L., Sworn, K., Turner, K. M., Yardley, L. & Hoddinott, P. (2020) 'Guidance for reporting intervention development studies in health research (GUIDED): an evidence-based consensus study'. *BMJ Open*, 10 (4), p. e033516 DOI: 10.1136/bmjopen-2019-033516.

Edmonds, M. E. & Foster, A. V. M. (2006) 'Diabetic foot ulcers'. *British Medical Journal*, 332 (7538), pp. 407-410.

Ehrmann, D., Spengler, M., Jahn, M., Niebuhr, D., Haak, T., Kulzer, B. & Hermanns, N. (2017) 'Adherence Over Time: The Course of Adherence to

Customized Diabetic Insoles as Objectively Assessed by a Temperature Sensor'. *Journal of Diabetes Science and Technology*, 12 (3), pp. 695-700.

Eid, S., Sas, K. M., Abcouwer, S. F., Feldman, E. L., Gardner, T. W., Pennathur, S. & Fort, P. E. (2019) 'New insights into the mechanisms of diabetic complications: role of lipids and lipid metabolism'. *Diabetologia*, 62 (9), pp. 1539-1549.

Eldridge, S. M., Chan, C. L., Campbell, M. J., Bond, C. M., Hopewell, S., Thabane, L. & Lancaster, G. A. (2016a) 'CONSORT 2010 statement: extension to randomised pilot and feasibility trials'. *British Medical Journal*, 355 p. i5239 DOI: 10.1136/bmj.i5239 (Accessed: Oct 24).

Eldridge, S. M., Lancaster, G. A., Campbell, M. J., Thabane, L., Hopewell, S., Coleman, C. L. & Bond, C. M. (2016b) 'Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework'. *PLoS One*, 11 (3), pp. e0150205.

Elveru, R. A., Rothstein, J. M., Lamb, R. L. & Riddle, D. L. (1988) 'Methods for taking subtalar joint measurements'. *Physical therapy*, 68 (5), pp. 678-682.

Ermete, R. (2012) 'Clinical trials and communicating safely'. *Clinical Journal of Oncology Nursing*, 16 (1), pp. 25-27.

Estcourt, S., Epton, J., Epton, T., Vaidya, B. & Daly, M. (2016) 'Exploring the motivations of patients with type 2 diabetes to participate in clinical trials: a qualitative analysis'. *Research Involvement and Engagement*, 2 (1), p. 34 DOI: 10.1186/s40900-016-0050-y (Accessed: 2016/12/12).

Etikan, I., Musa, S. A. & Alkassim, R. S. (2016) 'Comparison of convenience sampling and purposive sampling'. *American journal of theoretical and applied statistics*, 5 (1), pp. 1-4.

Farrell, B., Kenyon, S. & Shakur, H. (2010) 'Managing clinical trials'. *Trials*, 11 (1), p. 78 DOI: 10.1186/1745-6215-11-78 [Online]. Available at: https://doi.org/10.1186/1745-6215-11-78 (Accessed: 2010/07/13).

Faulí, A. C., Andrés, C. L., Rosas, N. P., Fernández, M. J., Parreño, E. M. & Barceló, C. O. (2008) 'Physical evaluation of insole materials used to treat the diabetic foot'. *Journal of the American Medical Association*, 98 (3), pp. 229-238.

Feng, Y., Schlösser, F. J. & Sumpio, B. E. (2009) 'The Semmes Weinstein monofilament examination as a screening tool for diabetic peripheral neuropathy'. *Journal of vascular surgery*, 50 (3), pp. 675-682.

Fernandez, M. L. G., Lozano, R. M., Diaz, M. I. G.-Q., Jurado, M. A. G., Hernandez, D. M. & Montesinos, J. V. B. (2013) 'How effective is orthotic

treatment in patients with recurrent diabetic foot ulcers?'. *Journal Of The American Podiatry Association*, 103 (4), pp. 281-290.

Fernando, D. J., Masson, E. A., Veves, A. & Boulton, A. J. (1991) 'Relationship of limited joint mobility to abnormal foot pressures and diabetic foot ulceration'. *Diabetes Care*, 14 (1), pp. 8-11.

Fernando, M., Crowther, R., Lazzarini, P., Sangla, K., Cunningham, M., Buttner, P. & Golledge, J. (2013) 'Biomechanical characteristics of peripheral diabetic neuropathy: a systematic review and meta-analysis of findings from the gait cycle, muscle activity and dynamic barefoot plantar pressure'. *Clinical Biomechanics*, 28 (8), pp. 831-845.

Fernando, M. E., Crowther, R. G., Lazzarini, P. A., Sangla, K. S., Wearing, S., Buttner, P. & Golledge, J. (2019) 'Gait in people with nonhealing diabetes-related plantar ulcers'. *Physical therapy*, 99 (12), pp. 1602-1615.

Fogel, D. B. (2018) 'Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review'. *Contemporary Clinical Trials Communications*, 11 pp. 156-164.

Forbes, J. M. & Cooper, M. E. (2013) 'Mechanisms of diabetic complications'. *Physiological Reviews*, 93 (1), pp. 137-188.

Francis, J. J., O'Connor, D. & Curran, J. (2012) 'Theories of behaviour change synthesised into a set of theoretical groupings: introducing a thematic series on the theoretical domains framework'. *Implementation Science*, 7 (1), p. 35 DOI: 10.1186/1748-5908-7-35 [Online]. Available at: https://doi.org/10.1186/1748-5908-7-35 (Accessed: 2012/04/24).

Franz, J. R. (2016) 'The age-associated reduction in propulsive power generation in walking'. *Exercise And Sport Sciences Reviews*, 44 (4), pp. 129-136.

Frykberg, R. G., Bailey, L. F., Matz, A., Panthel, L. A. & Ruesch, G. (2002) 'Offloading properties of a rocker insole. A preliminary study'. *Journal Of The American Podiatry Association*, 92 (1), pp. 48-53.

Frykberg, R. G., Lavery, L. A., Pham, H., Harvey, C., Harkless, L. & Veves, A. (1998) 'Role of neuropathy and high foot pressures in diabetic foot ulceration'. *Diabetes Care*, 21 (10), pp. 1714-1719.

Fuller, E. A. (1999) 'Center of pressure and its theoretical relationship to foot pathology'. *Journal Of The American Podiatry Association*, 89 (6), pp. 278-291.

Game, F. L., Apelqvist, J., Attinger, C., Hartemann, A., Hinchliffe, R. J., Löndahl, M., Price, P. E., Jeffcoate, W. J. & International Working Group on the Diabetic, F. (2016) 'Effectiveness of interventions to enhance healing of chronic

ulcers of the foot in diabetes: a systematic review'. *Diabetes/metabolism research and reviews*, 32

Gefen, A. (2003) 'Plantar soft tissue loading under the medial metatarsals in the standing diabetic foot'. *Medical Engineering and Physics*, 25 (6), pp. 491-499.

Gethin, G., Probst, S., Stryja, J., Christiansen, N. & Price, P. (2020) 'Evidence for person-centred care in chronic wound care: A systematic review and recommendations for practice'. *The Journal of Wound Care*, 29 (Sup9b), pp. S1-S22.

Giacco, F. & Brownlee, M. (2010) 'Oxidative stress and diabetic complications'. *Circulation Research*, 107 (9), pp. 1058-1070.

Giacomozzi, C., Caselli, A., Macellari, V., Giurato, L., Lardieri, L. & Uccioli, L. (2002) 'Walking strategy in diabetic patients with peripheral neuropathy'. *Diabetes Care*, 25 (8), pp. 1451-1457.

Giacomozzi, C. & Martelli, F. (2006) 'Peak pressure curve: an effective parameter for early detection of foot functional impairments in diabetic patients'. *Gait Posture*, 23 (4), pp. 464-470.

Giacomozzi, C. & Vaclav, K. (2011) 'Potentialities and criticalities of plantar pressure measurements in the study of foot biomechanics: Devices, methodologies and applications'. *Biomechanics in applications*, 1 pp. 249-274.

Gibbons, C. H., Illigens, B. M., Wang, N. & Freeman, R. (2009) 'Quantification of sweat gland innervation: a clinical-pathologic correlation'. *Journal Of Neurology*, 72 (17), pp. 1479-1486.

Gilbey, S. G. (2004) 'Neuropathy and foot problems in diabetes'. *Clinical Medicine & Research*, 4 (4), pp. 318-323.

Gold, S. M., Enck, P., Hasselmann, H., Friede, T., Hegerl, U., Mohr, D. C. & Otte, C. (2017) 'Control conditions for randomised trials of behavioural interventions in psychiatry: a decision framework'. *The Lancet Psychiatry*, 4 (9), pp. 725-732.

Goodridge, D., Trepman, E. & Embil, J. M. (2005) 'Health-related quality of life in diabetic patients with foot ulcers: literature review'. *Journal of Wound Ostomy & Continence Nursing*, 32 (6), pp. 368-377.

Green, J., Willis, K., Hughes, E., Small, R., Welch, N., Gibbs, L. & Daly, J. (2007) 'Generating best evidence from qualitative research: the role of data analysis'. *Australian And New Zealand Journal Of Public Health*, 31 (6), pp. 545-550.

Greenhalgh, T. (2020) 'Will COVID-19 be evidence-based medicine's nemesis?'. *PLoS Medicine*, 17 (6), pp. e1003266-e1003266 *PubMed* DOI: 10.1371/journal.pmed.1003266.

Greenhalgh, T. & Papoutsi, C. (2018) 'Studying complexity in health services research: desperately seeking an overdue paradigm shift'. *BMC Medicine*, 16 (1), p. 95 DOI: 10.1186/s12916-018-1089-4 [Online]. Available at: https://doi.org/10.1186/s12916-018-1089-4 (Accessed: 2018/06/20).

Grouios, G. (2004) 'Corns and calluses in athletes' feet: a cause for concern'. *The Foot*, 14 (4), pp. 175-184.

Guldemond, N. A., Leffers, P., Schaper, N. C., Sanders, A. P., Nieman, F., Willems, P. & Walenkamp, G. H. I. M. (2007) 'The effects of insole configurations on forefoot plantar pressure and walking convenience in diabetic patients with neuropathic feet'. *Clinical Biomechanics*, 22 (1), pp. 81-87.

Gwak, Y., Kim, J., Lee, K. M. & Koo, S. (2020) 'Increase of stiffness in plantar fat tissue in diabetic patients'. *Journal of Biomechanics*, 107 p. 109857 DOI: 10.1016/j.jbiomech.2020.109857.

Gyure, M. E., Quillin, J. M., Rodríguez, V. M., Markowitz, M. S., Corona, R., Borzelleca, J., Jr., Bowen, D. J., Krist, A. H. & Bodurtha, J. N. (2014) 'Practical

Considerations for Implementing Research Recruitment Etiquette'. *IRB*, 36 (6), pp. 7-12.

Hamatani, M., Mori, T., Oe, M., Noguchi, H., Takehara, K., Amemiya, A., Ohashi, Y., Ueki, K., Kadowaki, T. & Sanada, H. (2016) 'Factors Associated With Callus in Patients with Diabetes, Focused on Plantar Shear Stress During Gait'. *Journal of Diabetes Science and Technology*, 10 (6), pp. 1353-1359.

Harding, K., Lynch, L., Porter, J. & Taylor, N. F. (2017) 'Organisational benefits of a strong research culture in a health service: a systematic review'. *Australian Health Review*, 41 (1), pp. 45-53.

Harding, K. E., Porter, J., Horne-Thompson, A., Donley, E. & Taylor, N. F. (2014) 'Not enough time or a low priority? Barriers to evidence-based practice for allied health clinicians'. *Journal of Continuing Education in the Health Professions*, 34 (4), pp. 224-231.

Hastings, M. K., Mueller, M. J., Pilgram, T. K., Lott, D. J., Commean, P. K. & Johnson, J. E. (2007) 'Effect of Metatarsal Pad Placement on Plantar Pressure in People with Diabetes Mellitus and Peripheral Neuropathy'. *Foot & Ankle International*, 28 (1), pp. 84.

Hathcoat, J. D., Meixner, C. & Nicholas, M. C. (2017) 'Ontology and Epistemology', in Liamputtong, P. (ed.) *Handbook of Research Methods in Health Social Sciences.* Singapore: Springer Singapore, pp. 1-19.

Hazari, A., Maiya, A. G., Shivashankara, K., Agouris, I., Monteiro, A., Jadhav, R., Kumar, S., Kumar, C. S. & Mayya, S. S. (2016) 'Kinetics and kinematics of diabetic foot in type 2 diabetes mellitus with and without peripheral neuropathy: a systematic review and meta-analysis'. *Springerplus*, 5 (1), p. 1819 DOI: 10.1186/s40064-016-3405-9.

He, Z., Tang, X., Yang, X., Guo, Y., George, T. J., Charness, N., Quan Hem, K. B., Hogan, W. & Bian, J. (2020) 'Clinical Trial Generalizability Assessment in the Big Data Era: A Review'. *Clinical And Translational Science*, 13 (4), pp. 675-684.

Healy, A., Dunning, D. N. & Chockalingam, N. (2011) 'Effect of insole material on lower limb kinematics and plantar pressures during treadmill walking'. *Prosthetics & Orthotics International (Taylor & Francis Ltd)*, 36 (1), pp. 53-62.

Hellstrand Tang, U., Zugner, R., Lisovskaja, V., Karlsson, J., Hagberg, K. & Tranberg, R. (2014) 'Comparison of plantar pressure in three types of insole given to patients with diabetes at risk of developing foot ulcers - A two-year, randomized trial'. *Journal of Clinical and Translational Endocrinology*, 1 (4), pp. 121-132.

Heneghan, C., Goldacre, B. & Mahtani, K. R. (2017) 'Why clinical trial outcomes fail to translate into benefits for patients'. *Trials*, 18 (1), pp. 122.

Henshall, C., Narendran, P., Andrews, R. C., Daley, A., Stokes, K. A., Kennedy, A. & Greenfield, S. (2018) 'Qualitative study of barriers to clinical trial retention in adults with recently diagnosed type 1 diabetes'. *BMJ Open*, 8 (7), pp. e022353.

Herbert, R., Jamtvedt, G., Hagen, K. B., Mead, J. & Chalmers, I. (2011) *Practical Evidence-Based Physiotherapy-E-Book.* Elsevier Health Sciences.

Heuch, L. & Streak Gomersall, J. (2016) 'Effectiveness of offloading methods in preventing primary diabetic foot ulcers in adults with diabetes: a systematic review'. *JBI Database of Systematic Reviews and Implementation Reports*, 14 (7), pp. 236-265.

Hinchliffe, R. J., Brownrigg, J. R., Andros, G., Apelqvist, J., Boyko, E. J., Fitridge, R., Mills, J. L., Reekers, J., Shearman, C. P., Zierler, R. E. & Schaper, N. C. (2016) 'Effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral artery disease: a systematic review'. *Diabetes/Metabolism Research & Reviews*, 32 Suppl 1 pp. 136-144.

Hingorani, A., LaMuraglia, G. M., Henke, P., Meissner, M. H., Loretz, L., Zinszer, K. M., Driver, V. R., Frykberg, R., Carman, T. L., Marston, W., Mills, J. L., Sr. & Murad, M. H. (2016) 'The management of diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine'. *Journal of vascular surgery*, 63 (2 Suppl), pp. 3s-21s.

Ho, C. Y. & Shanahan, C. M. (2016) 'Medial Arterial Calcification'. *Arteriosclerosis, Thrombosis, And Vascular Biology*, 36 (8), pp. 1475-1482.

Hoddinott, P. (2015) 'A new era for intervention development studies'. *Pilot and Feasibility Studies*, 1 (1), p. 36 DOI: 10.1186/s40814-015-0032-0 (Accessed: 2015/10/26).

Hoddinott, P., Pollock, A., O'Cathain, A., Boyer, I., Taylor, J., MacDonald, C., Oliver, S. & Donovan, J. L. (2018) 'How to incorporate patient and public perspectives into the design and conduct of research'. *Research*, 7 pp. 752-752 *PubMed* DOI: 10.12688/f1000research.15162.1.

Hoffmann, T. C., Glasziou, P. P., Boutron, I., Milne, R., Perera, R., Moher, D., Altman, D. G., Barbour, V., Macdonald, H., Johnston, M., Lamb, S. E., Dixon-Woods, M., McCulloch, P., Wyatt, J. C., Chan, A. W. & Michie, S. (2014) 'Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide'. *British Medical Journal*, 348 pp. g1687.

Horner, S., Rew, L. & Torres, R. (2006) 'Enhancing intervention fidelity: a means of strengthening study impact'. *Journal for Specialists in Pediatric Nursing*, 11 (2), pp. 80-89.

Horng, S. & Miller, F. G. (2003) 'Ethical framework for the use of sham procedures in clinical trials'. *Critical Care Medicine*, 31 (3), pp. S126-S130.

Horst, F., Mildner, M. & Schöllhorn, W. (2017) 'One-year persistence of individual gait patterns identified in a follow-up study–A call for individualised diagnose and therapy'. *Gait Posture*, 58 pp. 476-480.

Hróbjartsson, A., Emanuelsson, F., Skou Thomsen, A. S., Hilden, J. & Brorson, S. (2014) 'Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies'. *International Journal Of Epidemiology*, 43 (4), pp. 1272-1283.

Hróbjartsson, A., Thomsen, A. S. S., Emanuelsson, F., Tendal, B., Hilden, J., Boutron, I., Ravaud, P. & Brorson, S. (2012) 'Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors'. *British Medical Journal*, 344 p. e1119 DOI: 10.1136/bmj.e1119 [Online]. Available at: https://www.bmj.com/content/bmj/344/bmj.e1119.full.pdf.

Hsi, W., Chai, H. & Lai, J. (2002) 'Comparison of pressure and time parameters in evaluating diabetic footwear'. *American Journal of Physical Medicine & Rehabilitation*, 81 (11), pp. 822-829.

Hsi, W., Chai, H. & Lai, J. (2004) 'Evaluation of rocker sole by pressure-time curves in insensate forefoot during gait'. *American Journal of Physical Medicine & Rehabilitation*, 83 (7), pp. 500-506.

Hsiao, H., Guan, J. & Weatherly, M. (2002) 'Accuracy and precision of two in-shoe pressure measurement systems'. *ERGONOMICS*, 45 (8), pp. 537-555.

Ince, P., Kendrick, D., Game, F. & Jeffcoate, W. (2007) 'The association between baseline characteristics and the outcome of foot lesions in a UK population with diabetes'. *Diabetic Medicine*, 24 (9), pp. 977-981.

International Diabetes Federation (2020) 'IDF diabetes atlas, 8th Edition'. *Brussels, Belgium: International Diabetes Federation*. [Online]. Available at: https://www.diabetesatlas.org/en/ (Accessed: 16th June).

James, S., Abate, D., Abate, H. & Abay, S. M. (2018) 'Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017'. *Lancet*, 392 (10159), pp. 1789-1858.

Jarl, G. (2018) 'Methodological considerations of investigating adherence to using offloading devices among people with diabetes'. *Patient Preference And Adherence*, 12 pp. 1767-1775.

Jeffcoate, W. J., Bus, S. A., Game, F. L., Hinchliffe, R. J., Price, P. E. & Schaper, N. C. (2016) 'Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality'. *The lancet Diabetes & endocrinology*, 4 (9), pp. 781-788.

Jeffcoate, W. J., Chipchase, S. Y., Ince, P. & Game, F. L. (2006) 'Assessing the outcome of the management of diabetic foot ulcers using ulcer-related and person-related measures'. *Diabetes Care*, 29 (8), pp. 1784-1787.

Jeffcoate, W. J., Vileikyte, L., Boyko, E. J., Armstrong, D. G. & Boulton, A. J. M. (2018) 'Current Challenges and Opportunities in the Prevention and Management of Diabetic Foot Ulcers'. *Diabetes Care*, 41 (4), pp. 645-652.

Jeong, H.-J., Mueller, M. J., Zellers, J. A. & Hastings, M. K. (2021) 'Midfoot and ankle motion during heel rise and gait are related in people with diabetes and peripheral neuropathy'. *Gait Posture*, 84 pp. 38-44.

Johnson, M. O. & Remien, R. H. (2003) 'Adherence to research protocols in a clinical context: Challenges and recommendations from behavioral intervention trials'. *American Journal of Psychotherapy*, 57 (3), pp. 348-360.

Johnson, R. B. & Onwuegbuzie, A. J. (2004) 'Mixed Methods Research: A Research Paradigm Whose Time Has Come'. *Educational Researcher*, 33 (7), pp. 14-26.

Kallio, H., Pietilä, A. M., Johnson, M. & Kangasniemi, M. (2016) 'Systematic methodological review: developing a framework for a qualitative semi-structured interview guide'. *Journal of advanced nursing*, 72 (12), pp. 2954-2965.

Kang, M., Ragan, B. G. & Park, J.-H. (2008) 'Issues in outcomes research: an overview of randomization techniques for clinical trials'. *Journal of Athletic Training (National Athletic Trainers' Association)*, 43 (2), pp. 215-221.

Kastenbauer, T., Sokol, G., Auinger, M. & Irsigler, K. (1998) 'Running shoes for relief of plantar pressure in diabetic patients'. *Diabetic Medicine*, 15 (6), pp. 518-522.

Katoulis, E. C., Ebdon-Parry, M., Lanshammar, H., Vileikyte, L., Kulkarni, J. & Boulton, A. J. (1997) 'Gait abnormalities in diabetic neuropathy'. *Diabetes Care*, 20 (12), pp. 1904-1907.

Kearney, A., Rosala- Hallas, A., Bacon, N., Daykin, A., Shaw, A. R. G., Lane, A. J., Blazeby, J. M., Clarke, M., Williamson, P. R. & Gamble, C. (2018) 'Reducing attrition within clinical trials: The communication of retention and withdrawal within patient information leaflets'. *PLoS One*, 13 (10), pp. e0204886.

Keenan, A.-M., Redmond, A. C., Horton, M., Conaghan, P. G. & Tennant, A. (2007) 'The Foot Posture Index: Rasch analysis of a novel, foot-specific outcome measure'. *Archives of Physical Medicine & Rehabilitation*, 88 (1), pp. 88-93.

Kennedy-Martin, T., Curtis, S., Faries, D., Robinson, S. & Johnston, J. (2015) 'A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results'. *Trials*, 16 (1), p. 495 DOI: 10.1186/s13063-015-1023-4 [Online]. Available at: https://doi.org/10.1186/s13063-015-1023-4 (Accessed: 2015/11/03).

Kerr, C., Nixon, A. & Wild, D. (2010) 'Assessing and demonstrating data saturation in qualitative inquiry supporting patient-reported outcomes research'. *Expert Review Of Pharmacoeconomics & Outcomes Research*, 10 (3), pp. 269-281.

Kerr, M. (2017) *Foot care in diabetes: the human and financial cost.* NICE. Available at:

https://www.evidence.nhs.uk/document?id=1915227&returnUrl=Search%3Fq%3DDiabetic%2BAmputation&q=Diabetic+Amputation.

Kerr, M., Barron, E., Chadwick, P., Evans, T., Kong, W., Rayman, G., Sutton-Smith, M., Todd, G., Young, B. & Jeffcoate, W. (2019) 'The cost of diabetic foot ulcers and amputations to the National Health Service in England'. *Diabetic Medicine*, 36 (8), pp. 995-1002.

Khasnis, A. & Gokula, R. (2003) 'Romberg's test'. *Journal of Postgraduate Medicine*, 49 (2), pp. 169-172.

Khunkaew, S., Fernandez, R. & Sim, J. (2019) 'Health-related quality of life among adults living with diabetic foot ulcers: a meta-analysis'. *Qualitative health research*, 28 (6), pp. 1413-1427.

Kim, M. O., Coiera, E. & Magrabi, F. (2017) 'Problems with health information technology and their effects on care delivery and patient outcomes: a systematic review'. *Journal of the American Medical Informatics Association*, 24 (2), pp. 246-250.

Kirby, K. A. (2001) 'Subtalar joint axis location and rotational equilibrium theory of foot function'. *Journal Of The American Podiatry Association*, 91 (9), pp. 465-487.

Knowles, E. A. & Boulton, A. J. M. (1996) 'Do People With Diabetes Wear Their Prescribed Footwear?'. *Diabetic Medicine*, 13 (12), pp. 1064-1068.

Koch, M. (1993) '[Measuring plantar pressure in conventional shoes with the TEKSCAN sensory system]'. *Biomedical Engineering*, 38 (10), pp. 243-248.

Koch, T. (1998) 'Story telling: is it really research?'. *Journal of advanced nursing*, 28 (6), pp. 1182-1190.

Koo, T. K. & Li, M. Y. (2016) 'A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research'. *Journal of Chiropractic Medicine*, 15 (2), pp. 155-163.

Kossioris, A., Tentolouris, N., Kyriazopoulou, V., Loupa, C. V., Markou, G., Marakomichelakis, G. E., Zouridaki, E. & Tyllianakis, M. (2017) 'Initial and continued adherence to wearing appropriate footwear in people with diabetic foot disease: results of a pilot study'. *Hellenic Journal of Nursing Science*, 10 (4), pp. 21-28.

Lachin, J. M., Matts, J. P. & Wei, L. (1988) 'Randomization in clinical trials: conclusions and recommendations'. *Controlled Clinical Trials*, 9 (4), pp. 365-374.

Lalli, P., Chan, A., Garven, A., Midha, N., Chan, C., Brady, S., Block, E., Hu, B. & Toth, C. (2013) 'Increased gait variability in diabetes mellitus patients with neuropathic pain'. *Journal of Diabetes and its Complications*, 27 (3), pp. 248-254.

Lavery, L. A., Armstrong, D. G., Wunderlich, R. P., Tredwell, J. & Boulton, A. J. (2003) 'Predictive value of foot pressure assessment as part of a population-based diabetes disease management program'. *Diabetes Care*, 26 (4), pp. 1069-1073.

Lavery, L. A., Lafontaine, J., Higgins, K. R., Lanctot, D. R. & Constantinides, G. (2012) 'Shear-reducing insoles to prevent foot ulceration in high-risk diabetic patients'. *Advances in Skin & Wound Care*, 25 (11), pp. 519-526.

Lazzarini, P. A., Crews, R. T., van Netten, J. J., Bus, S. A., Fernando, M. E., Chadwick, P. J. & Najafi, B. (2019) 'Measuring Plantar Tissue Stress in People With Diabetic Peripheral Neuropathy: A Critical Concept in Diabetic Foot Management'. *Journal of Diabetes Science and Technology*, 13 (5), pp. 869-880.

Lazzarini, P. A., Pacella, R. E., Armstrong, D. G. & van Netten, J. J. (2018) 'Diabetes-related lower-extremity complications are a leading cause of the global burden of disability'. *Diabetic Medicine*, 10.1111/dme.13680DOI: 10.1111/dme.13680 (Accessed: May 23).

Ledoux, W. R., Shofer, J. B., Cowley, M. S., Ahroni, J. H., Cohen, V. & Boyko, E. J. (2013) 'Diabetic foot ulcer incidence in relation to plantar pressure magnitude and measurement location'. *Journal of Diabetes and its Complications*, 27 (6), pp. 621-626.

Ledoux, W. R., Shofer, J. B., Smith, D. G., Sullivan, K., Assal, M. & Reiber, G. E. (2005) 'Relationship between foot type, foot deformity, and ulcer occurrence in the high-risk diabetic foot'. *Journal of rehabilitation research and development*, 42 (5), pp. 665-672.

Levati, S., Campbell, P., Frost, R., Dougall, N., Wells, M., Donaldson, C. & Hagen, S. (2016) 'Optimisation of complex health interventions prior to a randomised controlled trial: a scoping review of strategies used'. *Pilot and Feasibility Studies*, 2 (1), p. 17 DOI: 10.1186/s40814-016-0058-y [Online]. Available at: https://doi.org/10.1186/s40814-016-0058-y (Accessed: 2016/03/15).

Lewinson, R. T. & Stefanyshyn, D. J. (2015) 'Losing control over control conditions in knee osteoarthritis orthotic research'. *Contemporary Clinical Trials*, 42 pp. 258-259.

Lim, C.-Y. & In, J. (2019) 'Randomization in clinical studies'. *Korean Journal of Adult Nursing*, 72 (3), pp. 221-232.

Lin, T.-L., Sheen, H.-M., Chung, C.-T., Yang, S.-W., Lin, S.-Y., Luo, H.-J., Chen, C.-Y., Chan, I. C., Shih, H.-S. & Sheu, W. H.-H. (2013) 'The effect of removing plugs and adding arch support to foam based insoles on plantar pressures in people with diabetic peripheral neuropathy'. *Journal of foot and ankle research*, 6 (1), pp. 29-29.

Lincoln, N., Jeffcoate, W., Ince, P., Smith, M. & Radford, K. (2007) 'Validation of a new measure of protective footcare behaviour: the Nottingham Assessment of Functional Footcare (NAFF)'. *Practical Diabetes International*, 24 (4), pp. 207-211.

Linden, A. (2013) 'Assessing regression to the mean effects in health care initiatives'. *BMC Medical Research Methodology*, 13 (1), p. 119 DOI: 10.1186/1471-2288-13-119 [Online]. Available at: https://doi.org/10.1186/1471-2288-13-119 (Accessed: 2013/09/28).

Lobmann, R., Kayser, R., Kasten, G., Kasten, U., Kluge, K., Neumann, W. & Lehnert, H. (2001) 'Effects of preventative footwear on foot pressure as determined by pedobarography in diabetic patients: a prospective study'. *Diabetic Medicine*, 18 (4), pp. 314-319.

Lopez-Moral, M., Lazaro-Martinez, J. L., Garcia-Morales, E., Garcia-Alvarez, Y., JavierAlvaro-Afonso, F. & Molines-Barroso, R. J. (2019) 'Clinical efficacy of

therapeutic footwear with a rigid rocker sole in the prevention of recurrence in patients with diabetes mellitus and diabetic polineuropathy: A randomized clinical trial'. *PLoS One*, 14 (7), DOI: 10.1371/journal.pone.0219537.

Lott, D. J., Hastings, M. K., Commean, P. K., Smith, K. E. & Mueller, M. J. (2007) 'Effect of footwear and orthotic devices on stress reduction and soft tissue strain of the neuropathic foot'. *Clinical Biomechanics*, 22 (3), pp. 352-359.

Lott, D. J., Zou, D. & Mueller, M. J. (2008) 'Pressure gradient and subsurface shear stress on the neuropathic forefoot'. *Clinical Biomechanics*, 23 (3), pp. 342-348.

Luckie, R., Leese, G., McAlpine, R., MacEwen, C. J., Baines, P. S., Morris, A. D. & Ellis, J. D. (2007) 'Fear of visual loss in patients with diabetes: results of the prevalence of diabetic eye disease in Tayside, Scotland (P-DETS) study'. *Diabetic Medicine*, 24 (10), pp. 1086-1092.

Luo, Z. P., Berglund, L. J. & An, K. N. (1998) 'Validation of F-Scan pressure sensor system: a technical note'. *Journal of rehabilitation research and development*, 35 (2), pp. 186-191.

Lutjeboer, T., van Netten, J. J., Postema, K. & Hijmans, J. M. (2018) 'Validity and feasibility of a temperature sensor for measuring use and non-use of

orthopaedic footwear'. *Journal of Rehabilitation Medicine (Stiftelsen Rehabiliteringsinformation)*, 50 (10), pp. 920-926.

Marczak, D., Liberski, S. & Migdalski, A. (2018) 'Plantar calluses-pathogenesis, risk factors, prophylaxis, methods of treatment'. *Journal of Education, Health and Sport*, 8 (8), pp. 302-312.

Martin Bland, J. & Altman, D. (1986) 'Statistical methods for assessing agreement between two methods of clincal measurement'. *The Lancet*, 327 (8476), pp. 307-310.

Martinez-Santos, A., Preece, S. & Nester, C. J. (2019) 'Evaluation of orthotic insoles for people with diabetes who are at-risk of first ulceration'. *Journal of foot and ankle research*, 12 p. 35 DOI: 10.1186/s13047-019-0344-z.

Mathur, R., Palla, L., Farmer, R. E., Chaturvedi, N. & Smeeth, L. (2020) 'Ethnic differences in the severity and clinical management of type 2 diabetes at time of diagnosis: A cohort study in the UK Clinical Practice Research Datalink'. *Diabetes Research and Clinical Practice*, 160 pp. 108006.

Matts, J. P. & Lachin, J. M. (1988) 'Properties of permuted-block randomization in clinical trials'. *Controlled Clinical Trials*, 9 (4), pp. 327-344.

Mbuagbaw, L., Kosa, S. D., Lawson, D. O., Stalteri, R., Olaiya, O. R., Alotaibi, A. & Thabane, L. (2019) 'The reporting of progression criteria in protocols of pilot trials designed to assess the feasibility of main trials is insufficient: a meta-epidemiological study'. *Pilot and Feasibility Studies*, 5 (1), p. 120 DOI: 10.1186/s40814-019-0500-z [Online]. Available at: https://doi.org/10.1186/s40814-019-0500-z (Accessed: 2019/11/03).

McPherson, G. C., Campbell, M. K. & Elbourne, D. R. (2012) 'Use of randomisation in clinical trials: a survey of UK practice'. *Trials*, 13 p. 198 DOI: 10.1186/1745-6215-13-198 (Accessed: Oct 26).

McPoil, T. G. & Hunt, G. C. (1995) 'Evaluation and management of foot and ankle disorders: present problems and future directions'. *Journal of Orthopaedic & Sports Physical Therapy*, 21 (6), pp. 381-388.

Mehra, M., Kurpanek, K., Petrizzo, M., Brenner, S., McCracken, Y., Katz, T. & Gurian, M. (2014) 'The life cycle and management of protocol deviations'. *Therapeutic innovation & regulatory science*, 48 (6), pp. 762-777.

Meloni, M., Izzo, V., Giurato, L., Lázaro-Martínez, J. L. & Uccioli, L. (2020) 'Prevalence, Clinical Aspects and Outcomes in a Large Cohort of Persons with Diabetic Foot Disease: Comparison between Neuropathic and Ischemic Ulcers'. *Journal Of Clinical Medicine*, 9 (6), DOI: 10.3390/jcm9061780 (Accessed: Jun 8).

Michie, S., Brown, J., Geraghty, A. W. A., Miller, S., Yardley, L., Gardner, B., Shahab, L., McEwen, A., Stapleton, J. A. & West, R. (2012) 'Development of StopAdvisor: A theory-based interactive internet-based smoking cessation intervention'. *Translational Behavioral Medicine*, 2 (3), pp. 263-275.

Mohamed, O., Cerny, K., Rojek, L., Herbert, K., Turner, R. & Waistell, S. (2004) 'The Effects of Plastazote and Aliplast/Plastazote Orthoses on Plantar pressures in Elderly Persons With Diabetic Neuropathy'. *Journal of Prosthetics & Orthotics (JPO)*, 16 (2), pp. 55-63.

Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gotzsche, P. C., Devereaux, P. J., Elbourne, D., Egger, M. & Altman, D. G. (2010) 'CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials'. *Journal Of Clinical Epidemiology*, 63 (8), pp. e1-37.

Moher, D., Schulz, K. F. & Altman, D. G. (2001) 'The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials'. *Annals Of Medicine*, 134 (8), pp. 657-662.

Moon, K. & Blackman, D. (2014) 'A guide to understanding social science research for natural scientists'. *Conservation Biology*, 28 (5), pp. 1167-1177.

Moore, G. F., Audrey, S., Barker, M., Bond, L., Bonell, C., Hardeman, W., Moore, L., O'Cathain, A., Tinati, T., Wight, D. & Baird, J. (2015) 'Process evaluation of complex interventions: Medical Research Council guidance'. *British Medical Journal*, 350 p. h1258 DOI: 10.1136/bmj.h1258.

Morgan, B., Hejdenberg, J., Hinrichs-Krapels, S. & Armstrong, D. (2018) 'Do feasibility studies contribute to, or avoid, waste in research?'. *PLoS One*, 13 (4), pp. e0195951.

Morris, Z. S., Wooding, S. & Grant, J. (2011) 'The answer is 17 years, what is the question: understanding time lags in translational research'. *Journal of the Royal Society of Medicine*, 104 (12), pp. 510-520.

Moser, P. (2020) 'Out of Control? Managing Baseline Variability in Experimental Studies with Control Groups', in Bespalov, A., Michel, M.C. and Steckler, T. (eds.) *Good Research Practice in Non-Clinical Pharmacology and Biomedicine.* Cham: Springer International Publishing, pp. 101-117.

Mosteo, A. S., Spink, M. & Chuter, V. (2018) 'Validation of a weight bearing ankle equinus value in older adults with diabetes'. *Journal of foot and ankle research*, 11 (1), pp. 1-8.

Moustgaard, H., Clayton, G. L., Jones, H. E., Boutron, I., Jørgensen, L., Laursen, D. R. T., Olsen, M. F., Paludan-Müller, A., Ravaud, P., Savović, J.,

Sterne, J. A. C., Higgins, J. P. T. & Hróbjartsson, A. (2020) 'Impact of blinding on estimated treatment effects in randomised clinical trials: meta-epidemiological study'. *British Medical Journal*, 368 p. l6802 DOI: 10.1136/bmj.l6802 [Online]. Available at: https://www.bmj.com/content/bmj/368/bmj.l6802.full.pdf.

Mueller, M. & Strube, M. (1996a) 'Generalizability of in-shoe peak pressure measures using the F-scan system'. *Clinical Biomechanics*, 11 (3), pp. 159-164.

Mueller, M. J. (1996) 'Identifying patients with diabetes mellitus who are at risk for lower-extremity complications: use of Semmes-Weinstein monofilaments'. *Physical therapy*, 76 (1), pp. 68-71.

Mueller, M. J., Hastings, M., Commean, P. K., Smith, K. E., Pilgram, T. K., Robertson, D. & Johnson, J. (2003) 'Forefoot structural predictors of plantar pressures during walking in people with diabetes and peripheral neuropathy'. *Journal of Biomechanics*, 36 (7), pp. 1009-1017.

Mueller, M. J., Lott, D. J., Hastings, M. K., Commean, P. K., Smith, K. E. & Pilgram, T. K. (2006) 'Efficacy and mechanism of orthotic devices to unload metatarsal heads in people with diabetes and a history of plantar ulcers'. *Physical therapy*, 86 (6), pp. 833-842.

Mueller, M. J., Minor, S. D., Sahrmann, S. A., Schaaf, J. A. & Strube, M. J. (1994) 'Differences in the gait characteristics of patients with diabetes and peripheral neuropathy compared with age-matched controls'. *Physical therapy*, 74 (4), pp. 299-308.

Mueller, M. J. & Strube, M. J. (1996b) 'Generalizability of in-shoe peak pressure measures using the F-scan system'. *Clinical Biomechanics*, 11 (3), pp. 159-164.

Mueller, M. J., Zou, D., Bohnert, K. L., Tuttle, L. J. & Sinacore, D. R. (2008) 'Plantar stresses on the neuropathic foot during barefoot walking'. *Physical therapy*, 88 (11), pp. 1375-1384.

Murray, H. J., Young, M. J., Hollis, S. & Boulton, A. J. (1996) 'The association between callus formation, high pressures and neuropathy in diabetic foot ulceration'. *Diabetic Medicine*, 13 (11), pp. 979-982.

Mustapa, A., Justine, M., Mohd Mustafah, N., Jamil, N. & Manaf, H. (2016) 'Postural Control and Gait Performance in the Diabetic Peripheral Neuropathy: A Systematic Review'. *BioMed Research International*, 2016 pp. 9305025-9305025 *PubMed* DOI: 10.1155/2016/9305025.

Najafi, B., Reeves, N. D. & Armstrong, D. G. (2020) 'Leveraging smart technologies to improve the management of diabetic foot ulcers and extend

ulcer-free days in remission'. *Diabetes/Metabolism Research & Reviews*, 36 Suppl 1 pp. e3239.

Ndip, A., Lavery, L. A., LaFontaine, J., Rutter, M. K., Vardhan, A., Vileikyte, L. & Boulton, A. J. M. (2010) 'High Levels of Foot Ulceration and Amputation Risk in a Multiracial Cohort of Diabetic Patients on Dialysis Therapy'. *Diabetes Care*, 33 (4), pp. 878-880.

Nester, C. J., Graham, A., Martinez-Santos, A., Williams, A. E., McAdam, J., Newton, V., Sweeney, D. & Walker, D. (2018) 'National profile of foot orthotic provision in the United Kingdom, part 2: podiatrist, orthotist and physiotherapy practices'. *Journal of foot and ankle research*, 11 (1), pp. 10.

NICE (2015) 'Diabetic foot problems: prevention and management; NG19'. [Online]. Available at: https://www.nice.org.uk/guidance/ng19 (Accessed: 14th June).

Nicholson, G. P., Ferguson-Pell, M. W., Smith, K., Edgar, M. & Morley, T. (2003) 'The objective measurement of spinal orthosis use for the treatment of adolescent idiopathic scoliosis'. *Spine (Phila Pa 1976)*, 28 (19), pp. 2243-2250; discussion 2250-2241.

Nickinson, A. T. O., Bridgwood, B., Houghton, J. S. M., Nduwayo, S., Pepper, C., Payne, T., Bown, M. J., Davies, R. S. M. & Sayers, R. D. (2020) ' A

systematic review investigating the identification, causes, and outcomes of delays in the management of chronic limb-threatening ischemia and diabetic foot ulceration'. *Journal of vascular surgery*, 71 (2), pp. 669-681.

Nicolopoulos, C. S., Anderson, E. G., Solomonidis, S. E. & Giannoudis, P. V. (2000) 'Evaluation of the gait analysis FSCAN pressure system: clinical tool or toy?'. *The Foot*, 10 (3), pp. 124-130.

Nigg, B. M., Baltich, J., Hoerzer, S. & Enders, H. (2015) 'Running shoes and running injuries: mythbusting and a proposal for two new paradigms: 'preferred movement path' and 'comfort filter''. *BJSM*, 49 (20), pp. 1290-1294.

Nigg, B. M., Nurse, M. A. & Stefanyshyn, D. J. (1999) 'Shoe inserts and orthotics for sport and physical activities'. *Medicine & Science in Sports & Exercise*, 31 (7), pp. S421-S428.

NIHR (2019a) *Is an intervention ready for HTA researcher-led evaluation?* Available at: https://www.nihr.ac.uk/documents/is-an-intervention-ready-for-hta-researcher-led-evaluation/22003 (Accessed: 18 February 2021).

NIHR (2019b) 'INVOLVE: Research design services and public involvement'. INVOLVE [Online]. Available at: https://www.invo.org.uk/find-out-more/how-to-involve-people/ (Accessed: 20th July 2020).

Nouman, M., Dissaneewate, T., Leelasamran, W. & Chatpun, S. (2019) 'The insole materials influence the plantar pressure distributions in diabetic foot with neuropathy during different walking activities'. *Gait Posture*, 74 pp. 154-161.

Nouman, M., Leelasamran, W. & Chatpun, S. (2017) 'Effectiveness of Total Contact Orthosis for Plantar Pressure Redistribution in Neuropathic Diabetic Patients During Different Walking Activities'. *Foot & Ankle International*, 38 (8), pp. 901-908.

Nowell, L. S., Norris, J. M., White, D. E. & Moules, N. J. (2017) 'Thematic analysis: Striving to meet the trustworthiness criteria'. *International Journal of Qualitative Methods*, 16 (1), pp. 1609406917733847.

O'Cathain, A., Croot, L., Duncan, E., Rousseau, N., Sworn, K., Turner, K. M., Yardley, L. & Hoddinott, P. (2019) 'Guidance on how to develop complex interventions to improve health and healthcare'. *BMJ Open*, 9 (8), p. e029954 DOI: 10.1136/bmjopen-2019-029954 [Online]. Available at: https://bmjopen.bmj.com/content/bmjopen/9/8/e029954.full.pdf.

O'Cathain, A., Croot, L., Sworn, K., Duncan, E., Rousseau, N., Turner, K., Yardley, L. & Hoddinott, P. (2019) 'Taxonomy of approaches to developing interventions to improve health: a systematic methods overview'. *Pilot and Feasibility Studies*, 5 (1), p. 41 DOI: 10.1186/s40814-019-0425-6 [Online].

Available at: https://doi.org/10.1186/s40814-019-0425-6 (Accessed: 2019/03/12).

O'Cathain, A., Hoddinott, P., Lewin, S., Thomas, K. J., Young, B., Adamson, J., Jansen, Y. J. F. M., Mills, N., Moore, G. & Donovan, J. L. (2015) 'Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers'. *Pilot and Feasibility Studies*, 1 (1), p. 32 DOI: 10.1186/s40814-015-0026-y [Online]. Available at: https://doi.org/10.1186/s40814-015-0026-y (Accessed: 2015/09/07).

O'Cathain, A., Murphy, E. & Nicholl, J. (2010) 'Three techniques for integrating data in mixed methods studies'. *British Medical Journal*, 341 DOI: 10.1136/bmj.c4587.

Olem, D., Sharp, K. M. & Johnson, M. O. (2009) 'Challenges with engaging participants in behavioral intervention research trials'. *Open Access Journal of Clinical Trials*, 1 (Default), pp. 17-21.

Ong, F. & Wong, T. (2005) 'Analysis of dynamic foot pressure distribution and ground reaction forces', *Third International Conference on Experimental Mechanics and Third Conference of the Asian Committee on Experimental Mechanics*. International Society for Optics and Photonics, pp. 681-686.

Orlin, M. N. & McPoil, T. G. (2000) 'Plantar Pressure Assessment'. *Physical therapy*, 80 (4), pp. 399-409.

Orsmond, G. I. & Cohn, E. S. (2015) 'The Distinctive Features of a Feasibility Study: Objectives and Guiding Questions'. *OTJR: Occupation, Participation and Health*, 35 (3), pp. 169-177.

Ortega-Avila, A. B., Cervera-Garvi, P., Ramos-Petersen, L., Chicharro-Luna, E. & Gijon-Nogueron, G. (2019) 'Patient-Reported Outcome Measures for Patients with Diabetes Mellitus Associated with Foot and Ankle Pathologies: A Systematic Review'. *Journal Of Clinical Medicine*, 8 (2), DOI: 10.3390/jcm8020146 (Accessed: Jan 27).

Ory, M. G., Lipman, P. D., Karlen, P. L., Gerety, M. B., Stevens, V. J., Singh, M. A., Buchner, D. M. & Schechtman, K. B. (2002) 'Recruitment of older participants in frailty/injury prevention studies'. *Prevention Science*, 3 (1), pp. 1-22.

Owings, T. M., Apelqvist, J., Stenström, A., Becker, M., Bus, S. A., Kalpen, A., Ulbrecht, J. S. & Cavanagh, P. R. (2009) 'Plantar pressures in diabetic patients with foot ulcers which have remained healed'. *Diabetic Medicine*, 26 (11), pp. 1141-1146.

Owings, T. M., Woerner, J. L., Frampton, J. D., Cavanagh, P. R. & Botek, G. (2008) 'Custom therapeutic insoles based on both foot shape and plantar pressure measurement provide enhanced pressure relief'. *Diabetes Care*, 31 (5), pp. 839-844.

Oyibo, S. O., Jude, E. B., Tarawneh, I., Nguyen, H. C., Harkless, L. B. & Boulton, A. J. (2001) 'A comparison of two diabetic foot ulcer classification systems the Wagner and the University of Texas wound classification systems'. *Diabetes Care*, 24 (1), pp. 84-88.

Page, S. J. & Persch, A. C. (2013) 'Recruitment, retention, and blinding in clinical trials'. *The American journal of occupational therapy : official publication of the American Occupational Therapy Association*, 67 (2), pp. 154-161.

Pager, S., Holden, L. & Golenko, X. (2012) 'Motivators, enablers, and barriers to building allied health research capacity'. *Journal Of Multidisciplinary Healthcare*, 5 pp. 53-59.

Paisey, R. B., Abbott, A., Levenson, R., Harrington, A., Browne, D., Moore, J., Bamford, M., Roe, M. & team, t. S.-W. C. S. C. N. p. d. f. s. r. (2018) 'Diabetes-related major lower limb amputation incidence is strongly related to diabetic foot service provision and improves with enhancement of services: peer review of the South-West of England'. *Diabetic Medicine*, 35 (1), pp. 53-62.

Paisey, R. B., Abbott, A., Walker, D. & Paisey, C. F. (2019) 'Diabetic foot ulcer incidence and survival with improved diabetic foot services: an 18-year study'. *Diabetic Medicine*, 36 (11), pp. 1424-1430.

Palinkas, L. A., Horwitz, S. M., Green, C. A., Wisdom, J. P., Duan, N. & Hoagwood, K. (2015) 'Purposeful Sampling for Qualitative Data Collection and Analysis in Mixed Method Implementation Research'. *Administration and Policy in Mental Health and Mental Health Services Research*, 42 (5), pp. 533-544.

Park, J., Bang, H. & Cañette, I. (2008) 'Blinding in clinical trials, time to do it better'. *Complementary Therapies in Medicine*, 16 (3), pp. 121-123.

Parker, D. J., Martinez-Santos, A., Nester, C., Nuttall, G. H., Hugill, T., Bray, N. & Edwards, R. T. (2019) 'A randomised controlled trial and cost-consequence analysis of traditional and digital foot orthoses supply chains in a National Health Service setting: application to feet at risk of diabetic plantar ulceration'. *Journal of foot and ankle research*, 12 p. 2 DOI: 10.1186/s13047-018-0311-0.

Pataky, T. C., Mu, T., Bosch, K., Rosenbaum, D. & Goulermas, J. Y. (2012) 'Gait recognition: highly unique dynamic plantar pressure patterns among 104 individuals'. *Journal of The Royal Society Interface*, 9 (69), pp. 790-800.

Paton, J., Bruce, G., Jones, R. & Stenhouse, E. (2011) 'Effectiveness of insoles used for the prevention of ulceration in the neuropathic diabetic foot: a systematic review'. *Journal of Diabetes and its Complications*, 25 (1), pp. 52-62.

Paton, J., Glasser, S., Collings, R. & Marsden, J. (2016) 'Getting the right balance: Insole design alters static balance in people with diabetic neuropathy'. *Foot and Ankle Surgery*, 1 pp. 65-66.

Paton, J., Jones, R. B., Stenhouse, E. & Bruce, G. (2007) 'The physical characteristics of materials used in the manufacture of orthoses for patients with diabetes'. *Foot & Ankle International*, 28 (10), pp. 1057-1063 1057p.

Paton, J. S., Roberts, A., Bruce, G. K. & Marsden, J. (2014a) 'Patients' Experience of therapeutic footwear whilst living at risk of neuropathic diabetic foot ulceration: an interpretative phenomenological analysis (IPA)'. *Journal of foot and ankle research*, 7 (1), pp. 16.

Paton, J. S., Stenhouse, E., Bruce, G. & Jones, R. (2014b) 'A longitudinal investigation into the functional and physical durability of insoles used for the preventive management of neuropathic diabetic feet'. *Journal Of The American Podiatry Association*, 104 (1), pp. 50-57.

Paton, J. S., Stenhouse, E. A., Bruce, G., Zahra, D. & Jones, R. B. (2012) 'A comparison of customised and prefabricated insoles to reduce risk factors for

neuropathic diabetic foot ulceration: a participant-blinded randomised controlled trial'. *Journal of foot and ankle research*, 5 (1), p. 31 *cmedm* DOI: 10.1186/1757-1146-5-31.

Patton, M. Q. (1990) *Qualitative evaluation and research methods.* Thousand Oaks, CA, USA: SAGE Publications, inc.

Payne, C., Turner, D. & Miller, K. (2002) 'Determinants of plantar pressures in the diabetic foot'. *Journal of Diabetes and its Complications*, 16 (4), pp. 277-283.

Peltier, A., Goutman, S. A. & Callaghan, B. C. (2014) 'Painful diabetic neuropathy'. *British Medical Journal*, 348 p. g1799 DOI: 10.1136/bmj.g1799 (Accessed: May 6).

Pendsey, S. P. (2010) 'Understanding diabetic foot'. *International Journal Of Diabetes In Developing Countries*, 30 (2), pp. 75-79.

Perry, J. E., Ulbrecth, J. S., Derr, J. A. & Cavanagh, P. R. (1995) 'The use of running shoes to reduce plantar pressures in patients who have diabetes'. *Journal of Bone and Joint Surgery - Series A*, 77 (12), pp. 1819-1828.

Peters, K. & Halcomb, E. (2015) 'Interviews in qualitative research'. *Nurse researcher*, 22 (4), p. 6 DOI: 10.7748/nr.22.4.6.s2.

Petrie, J. R., Guzik, T. J. & Touyz, R. M. (2018) 'Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms'. *Canadian Journal of Cardiology*, 34 (5), pp. 575-584.

Petrovic, M., Deschamps, K., Verschueren, S. M., Bowling, F. L., Maganaris, C. N., Boulton, A. J. M. & Reeves, N. D. (2017) 'Altered leverage around the ankle in people with diabetes: A natural strategy to modify the muscular contribution during walking?'. *Gait Posture*, 57 pp. 85-90.

Pham, H., Armstrong, D. G., Harvey, C., Harkless, L. B., Giurini, J. M. & Veves, A. (2000) 'Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial'. *Diabetes Care*, 23 (5), pp. 606-611.

Pham, T. M., Carpenter, J. R., Morris, T. P., Sharma, M. & Petersen, I. (2019) 'Ethnic Differences in the Prevalence of Type 2 Diabetes Diagnoses in the UK: Cross-Sectional Analysis of the Health Improvement Network Primary Care Database'. *Clinical Epidemiology*, 11 pp. 1081-1088.

PHE (2019) *Diabetes foot care profiles.* Public Health England. Available at: https://fingertips.phe.org.uk/profile/diabetes-ft (Accessed: 9th September).

Pietrosimone, B., Seeley, M. K., Johnston, C., Pfeiffer, S. J., Spang, J. T. & Blackburn, J. T. (2019) 'Walking Ground Reaction Force Post-ACL

Reconstruction: Analysis of Time and Symptoms'. *MEDICINE AND SCIENCE IN SPORTS AND EXERCISE*, 51 (2), pp. 246-254.

Plano Clark, V. L., Schumacher, K., West, C., Edrington, J., Dunn, L. B., Harzstark, A., Melisko, M., Rabow, M. W., Swift, P. S. & Miaskowski, C. (2013) 'Practices for Embedding an Interpretive Qualitative Approach Within a Randomized Clinical Trial'. *Journal of mixed methods research*, 7 (3), pp. 219-242.

Poltawski, L., Norris, M. & Dean, S. (2014) 'Intervention fidelity: developing an experience-based model for rehabilitation research'. *Journal of Rehabilitation Medicine (Stiftelsen Rehabiliteringsinformation)*, 46 (7), pp. 609-615.

Pope, C. & Mays, N. (2006) 'Qualitative methods in health research', *Qualitative research in health care, 3rd ed.* Williston, VT, US: BMJ Books, pp. 1-11.

Pound, N., Chipchase, S., Treece, K., Game, F. & Jeffcoate, W. (2005) 'Ulcer-free survival following management of foot ulcers in diabetes'. *Diabetic Medicine*, 22 (10), pp. 1306-1309.

Praet, S. F. E. & Louwerens, J. W. K. (2003) 'The influence of shoe design on plantar pressures in neuropathic feet'. *Diabetes Care*, 26 (2), pp. 441-445.

Preece, S. J., Chapman, J. D., Braunstein, B., Bruggemann, G. P. & Nester, C. J. (2017) 'Optimisation of rocker sole footwear for prevention of first plantar ulcer: comparison of group-optimised and individually-selected footwear designs'. *Journal of foot and ankle research*, 10 p. 27 DOI: 10.1186/s13047-017-0208-3.

Public Health England (2015) 'Diabetes prevalence estimates for local populations.'. *Diabetes prevalence estimates for local populations.* [Online]. Available at: https://www.gov.uk/government/publications/diabetes-prevalence-estimates-for-local-populations (Accessed: 20th May).

Raja, B., Neptune, R. R. & Kautz, S. A. (2012) 'Quantifiable patterns of limb loading and unloading during hemiparetic gait: relation to kinetic and kinematic parameters'. *Journal of rehabilitation research and development*, 49 (9), pp. 1293.

Raspovic, A. (2013) 'Gait characteristics of people with diabetes-related peripheral neuropathy, with and without a history of ulceration'. *Gait Posture*, 38 (4), pp. 723-728.

Raspovic, A., Newcombe, L., Lloyd, J. & Dalton, E. (2000) 'Effect of customized insoles on vertical plantar pressures in sites of previous neuropathic ulceration in the diabetic foot'. *The Foot*, 10 (3), pp. 133-138.

Raza, M. Z., Bruhn, H. & Gillies, K. (2020) 'Dissemination of trial results to participants in phase III pragmatic clinical trials: an audit of trial investigators intentions'. *BMJ Open*, 10 (1), pp. e035730.

Redwood, S. & Gill, P. S. (2013) 'Under-representation of minority ethnic groups in research — call for action'. *British Journal of General Practice*, 63 (612), pp. 342-343.

Reeves, S., Kuper, A. & Hodges, B. D. (2008) 'Qualitative research methodologies: ethnography'. *British Medical Journal*, 337 p. a1020 DOI: 10.1136/bmj.a1020.

Reiber, G. E., Smith, D. G., Boone, D. A., del Aguila, M., Borchers, R. E., Mathews, D., Joseph, A. W. & Burgess, E. M. (1997) 'Design and pilot testing of the DVA/Seattle Footwear System for diabetic patients with foot insensitivity'. *Journal of rehabilitation research and development*, 34 (1), pp. 1-8.

Reiber, G. E., Smith, D. G., Wallace, C., Sullivan, K., Hayes, S., Vath, C., Maciejewski, M. L., Yu, O., Heagerty, P. J. & LeMaster, J. (2002) 'Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized controlled trial'. *The Journal of the American Medical Association*, 287 (19), pp. 2552-2558.

Reiber, G. E., Vileikyte, L., Boyko, E. d., Del Aguila, M., Smith, D. G., Lavery, L. A. & Boulton, A. (1999) 'Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings'. *Diabetes Care*, 22 (1), pp. 157-162.

Richards, D. A., Bazeley, P., Borglin, G., Craig, P., Emsley, R., Frost, J., Hill, J., Horwood, J., Hutchings, H. A. & Jinks, C. (2019) 'Integrating quantitative and qualitative data and findings when undertaking randomised controlled trials'. *BMJ Open*, 9 (11), p. e032081 DOI: 10.1136/bmjopen-2019-032081.

Rintala, T.-M., Jaatinen, P., Paavilainen, E. & Åstedt-Kurki, P. (2013) 'Interrelation Between Adult Persons With Diabetes and Their Family:A Systematic Review of the Literature'. *Journal of Family Nursing*, 19 (1), pp. 3-28.

Ristikj-Stomnaroska, D., Risteska-Nejashmikj, V. & Papazova, M. (2019) 'Role of Inflammation in the Pathogenesis of Diabetic Peripheral Neuropathy'. *Open Access Macedonian Journal Of Medical Sciences*, 7 (14), pp. 2267-2270.

Rizzo, L., Tedeschi, A., Fallani, E., Coppelli, A., Vallini, V., Iacopi, E. & Piaggesi, A. (2012) 'Custom-made orthesis and shoes in a structured follow-up program reduces the incidence of neuropathic ulcers in high-risk diabetic foot patients'. *International Journal of Lower Extremity Wounds*, 11 (1), pp. 59-64.

Rolfe, G. (2006) 'Validity, trustworthiness and rigour: quality and the idea of qualitative research'. *Journal of advanced nursing*, 53 (3), pp. 304-310.

Rome, K. (1991) 'A study of the properties of materials used in podiatry'. *Journal Of The American Podiatry Association*, 81 (2), pp. 73-83.

Root, M. (1973) 'Biomechanical examination of the foot'. *Journal Of The American Podiatry Association*, 63 (1), pp. 28-29.

Rosland, A.-M., Kieffer, E., Israel, B., Cofield, M., Palmisano, G., Sinco, B., Spencer, M. & Heisler, M. (2008) 'When Is Social Support Important? The Association of Family Support and Professional Support with Specific Diabetes Self-management Behaviors'. *Journal Of General Internal Medicine*, 23 (12), p. 1992 DOI: 10.1007/s11606-008-0814-7 [Online]. Available at: https://doi.org/10.1007/s11606-008-0814-7 (Accessed: 2008/10/15).

Roth, A. D., Pilling, S. & Turner, J. (2010) 'Therapist Training and Supervision in Clinical Trials: Implications for Clinical Practice'. *Behavioural and Cognitive Psychotherapy*, 38 (3), pp. 291-302.

Rothwell, P. M. (2005) 'External validity of randomised controlled trials: "to whom do the results of this trial apply?"'. *Lancet*, 365 (9453), pp. 82-93.

Rubinstein, L. V., Korn, E. L., Freidlin, B., Hunsberger, S., Ivy, S. P. & Smith, M. A. (2005) 'Design issues of randomized phase II trials and a proposal for phase II screening trials'. *Journal of Clinical Oncology*, 23 (28), pp. 7199-7206.

Sacco, I. C., Akashi, P. M. & Hennig, E. M. (2010) 'A comparison of lower limb EMG and ground reaction forces between barefoot and shod gait in participants with diabetic neuropathic and healthy controls'. *BMC Musculoskelet Disord*, 11 p. 24 *rzh* DOI: 10.1186/1471-2474-11-24.

Saluja, S., Anderson, S. G., Hambleton, I., Shoo, H., Livingston, M., Jude, E. B., Lunt, M., Dunn, G. & Heald, A. H. (2020) 'Foot ulceration and its association with mortality in diabetes mellitus: a meta-analysis'. *Diabetic Medicine*, 37 (2), pp. 211-218.

Sandelowski, M. (1993) 'Rigor or rigor mortis: the problem of rigor in qualitative research revisited'. *Advances in Nursing Science*, 16 (2), pp. 1-8.

Sas, K. M., Kayampilly, P., Byun, J., Nair, V., Hinder, L. M., Hur, J., Zhang, H., Lin, C., Qi, N. R. & Michailidis, G. (2016) 'Tissue-specific metabolic reprogramming drives nutrient flux in diabetic complications'. *JCI insight*, 1 (15), DOI: 10.1172/jci.insight.86976.

Savelberg, H. H., Schaper, N. C., Willems, P. J., De Lange, T. L. & Meijer, K. (2009) 'Redistribution of joint moments is associated with changed plantar pressure in diabetic polyneuropathy'. *BMC Musculoskelet Disord*, 10 (1), pp. 16.

Schaper, N. C., van Netten, J. J., Apelqvist, J., Bus, S. A., Hinchliffe, R. J., Lipsky, B. A. & Board, I. E. (2020) 'Practical Guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update)'. *Diabetes/metabolism research and reviews*, 36 (S1), p. e3266 DOI: 10.1002/dmrr.3266.

Schenck, C. & Kesar, T. M. (2017) 'Effects of unilateral real-time biofeedback on propulsive forces during gait'. *Journal Of Neuroengineering And Rehabilitation*, 14 (1), pp. 52.

Scherer, P. R. (1975) 'A clinical study to determine the effects of wearing Earth Shoes'. *Journal Of The American Podiatry Association*, 65 (5), pp. 422-443.

Scotland, J. (2012) 'Exploring the philosophical underpinnings of research: Relating ontology and epistemology to the methodology and methods of the scientific, interpretive, and critical research paradigms'. *English language teaching*, 5 (9), pp. 9-16.

Scott, N. W., McPherson, G. C., Ramsay, C. R. & Campbell, M. K. (2002) 'The method of minimization for allocation to clinical trials: a review'. *Controlled Clinical Trials*, 23 (6), pp. 662-674.

Segal, A., Rohr, E., Orendurff, M., Shofer, J., O'Brien, M. & Sangeorzan, B. (2004) 'The effect of walking speed on peak plantar pressure'. *Foot & Ankle International*, 25 (12), pp. 926-933.

Senussi, M., Lincoln, N. & Jeffcoate, W. (2011) 'Psychometric Properties of the Nottingham Assessment of Functional Footcare (NAFF)'. *International Journal of Therapy and Rehabilitation*, 18 (6), pp. 330-334.

Shakespeare, T. P., Gebski, V. J., Veness, M. J. & Simes, J. (2001) 'Improving interpretation of clinical studies by use of confidence levels, clinical significance curves, and risk-benefit contours'. *The Lancet*, 357 (9265), pp. 1349-1353.

Shiell, A., Hawe, P. & Gold, L. (2008) 'Complex interventions or complex systems? Implications for health economic evaluation'. *British Medical Journal*, 336 (7656), pp. 1281-1283.

Shiovitz, T. M., Bain, E. E., McCann, D. J., Skolnick, P., Laughren, T., Hanina, A. & Burch, D. (2016) 'Mitigating the Effects of Nonadherence in Clinical Trials'. *Journal of Clinical Pharmacology*, 56 (9), pp. 1151-1164.

Shippee, N. D., Domecq Garces, J. P., Prutsky Lopez, G. J., Wang, Z., Elraiyah, T. A., Nabhan, M., Brito, J. P., Boehmer, K., Hasan, R. & Firwana, B. (2015) 'Patient and service user engagement in research: a systematic review and synthesized framework'. *Health Expectations*, 18 (5), pp. 1151-1166.

Sim, J. (2019) 'Should treatment effects be estimated in pilot and feasibility studies?'. *Pilot and Feasibility Studies*, 5 (1), p. 107 DOI: 10.1186/s40814-019-0493-7 [Online]. Available at: https://doi.org/10.1186/s40814-019-0493-7 (Accessed: 2019/08/28).

Sinacore, D. R., Gutekunst, D. J., Hastings, M. K., Strube, M. J., Bohnert, K. L., Prior, F. W. & Johnson, J. E. (2013) 'Neuropathic midfoot deformity: associations with ankle and subtalar joint motion'. *Journal of foot and ankle research*, 6 (1), p. 11 DOI: 10.1186/1757-1146-6-11 (Accessed: 2013/03/25).

Skea, Z. C., Newlands, R. & Gillies, K. (2019) 'Exploring non-retention in clinical trials: a meta-ethnographic synthesis of studies reporting participant reasons for drop out'. *BMJ Open*, 9 (6), pp. e021959.

Skea, Z. C., Treweek, S. & Gillies, K. (2017) ''It's trying to manage the work': a qualitative evaluation of recruitment processes within a UK multicentre trial'. *BMJ Open*, 7 (8), p. e016475 DOI: 10.1136/bmjopen-2017-016475 [Online]. Available at: https://bmjopen.bmj.com/content/bmjopen/7/8/e016475.full.pdf.

Skivington, K., Matthews, L., Craig, P., Simpson, S. & Moore, L. (2018) 'Developing and evaluating complex interventions: updating Medical Research Council guidance to take account of new methodological and theoretical approaches'. *The Lancet*, 392 p. S2 DOI: 10.1016/S0140-6736(18)32865-4.

Slade, S. C., Philip, K. & Morris, M. E. (2018) 'Frameworks for embedding a research culture in allied health practice: a rapid review'. *Health Research Policy and Systems*, 16 (1), p. 29 DOI: 10.1186/s12961-018-0304-2 [Online]. Available at: https://doi.org/10.1186/s12961-018-0304-2 (Accessed: 2018/03/21).

Slaughter, S. E., Hill, J. N. & Snelgrove-Clarke, E. (2015) 'What is the extent and quality of documentation and reporting of fidelity to implementation strategies: a scoping review'. *Implementation Science*, 10 (1), pp. 129.

Smith, J. & Firth, J. (2011) 'Qualitative data analysis: the framework approach'. *Nurse researcher*, 18 (2), pp. 52-62.

Snowdon, D. A., Leggat, S. G. & Taylor, N. F. (2017) 'Does clinical supervision of healthcare professionals improve effectiveness of care and patient experience? A systematic review'. *BMC Health Services Research*, 17 (1), p. 786 DOI: 10.1186/s12913-017-2739-5 [Online]. Available at: https://doi.org/10.1186/s12913-017-2739-5 (Accessed: 2017/11/28).

Soulier, S. M. (1986) 'The use of running shoes in the prevention of plantar diabetic ulcers'. *Journal Of The American Podiatry Association*, 76 (7), pp. 395-400.

Spieth, P. M., Kubasch, A. S., Penzlin, A. I., Illigens, B. M.-W., Barlinn, K. & Siepmann, T. (2016) 'Randomized controlled trials - a matter of design'. *Neuropsychiatric Disease And Treatment*, 12 pp. 1341-1349.

Spillane, V., Byrne, M. C., Byrne, M., Leathem, C. S., O'Malley, M. & Cupples, M. E. (2007) 'Monitoring treatment fidelity in a randomized controlled trial of a complex intervention'. *Journal of advanced nursing*, 60 (3), pp. 343-352.

Strom, J. L. & Egede, L. E. (2012) 'The Impact of Social Support on Outcomes in Adult Patients with Type 2 Diabetes: A Systematic Review'. *Current Diabetes Reports*, 12 (6), pp. 769-781.

Sun, J., Wang, Y., Zhang, X., Zhu, S. & He, H. (2020) 'Prevalence of peripheral neuropathy in patients with diabetes: A systematic review and meta-analysis'. *Primary Care Diabetes*, 14 (5), pp. 435-444.

Suresh, K. (2011) 'An overview of randomization techniques: An unbiased assessment of outcome in clinical research'. *Journal of Human Reproductive Sciences*, 4 (1), pp. 8-11.

Sutherland, E. R. (2007) 'Sham procedure versus usual care as the control in clinical trials of devices: which is better?'. *Proceedings of the American Thoracic Society*, 4 (7), pp. 574-576.

Tabue-Teguo, M., Perès, K., Simo, N., Le Goff, M., Perez Zepeda, M. U., Féart, C., Dartigues, J.-F., Amieva, H. & Cesari, M. (2020) 'Gait speed and body mass index: Results from the AMI study'. *PLoS One*, 15 (3), p. e0229979 DOI: 10.1371/journal.pone.0229979.

Tashakkori, A. & Creswell, J. W. (2007) *The new era of mixed methods.* Thousand Oaks, CA, USA: Sage Publications.

Tashakkori, A. & Teddlie, C. (2009) 'Integrating qualitative and quantitative approaches to research'. *The SAGE handbook of applied social research methods*, 2 pp. 283-317.

Taylor, J. (2019) 'Reporting research findings to participants is an ethical imperative'. *BMJ (Online)*, 367 DOI: 10.1136/bmj.l6324.

Telfer, S., Woodburn, J., Collier, A. & Cavanagh, P. R. (2017) 'Virtually optimized insoles for offloading the diabetic foot: A randomized crossover study'. *Journal of Biomechanics*, 60 pp. 157-161.

Temple, R. & Ellenberg, M. (2000) 'Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments. Part 1: Ethical and Scientific Issues'. *Annals Of Medicine*, 133 (6), pp. 455-463.

Tentolouris, N., Marinou, K., Kokotis, P., Karanti, A., Diakoumopoulou, E. & Katsilambros, N. (2009) 'Sudomotor dysfunction is associated with foot ulceration in diabetes'. *Diabetic Medicine*, 26 (3), pp. 302-305.

Tentolouris, N., Voulgari, C., Liatis, S., Kokkinos, A., Eleftheriadou, I., Makrilakis, K., Marinou, K. & Katsilambros, N. (2010) 'Moisture Status of the Skin of the Feet Assessed by the Visual Test Neuropad Correlates With Foot Ulceration in Diabetes'. *Diabetes Care*, 33 (5), pp. 1112-1114.

Thabane, L., Ma, J., Chu, R., Cheng, J., Ismaila, A., Rios, L. P., Robson, R., Thabane, M., Giangregorio, L. & Goldsmith, C. H. (2010) 'A tutorial on pilot studies: the what, why and how'. *BMC Medical Research Methodology*, 10 (1), pp. 1.

Thangaratinam, S. & Khan, K. S. (2015) 'Participation in research as a means of improving quality of care: the role of a principal investigator in multicentre clinical trials'. *The Obstetrician & Gynaecologist*, 17 (1), pp. 55-61.

Thoma, A. & Eaves, F. F., III (2017) 'To Get the Best Outcome, Choose the Best Outcome'. *Aesthetic Surgery Journal*, 37 (6), pp. 739-741.

Thompson, N., Gordey, L., Bowles, H., Parslow, N. & Houghton, P. (2013) 'Reliability and validity of the revised photographic wound assessment tool on digital images taken of various types of chronic wounds'. *Advances in Skin & Wound Care*, 26 (8), pp. 360-373.

Tickle-Degnen, L. (2013) 'Nuts and bolts of conducting feasibility studies'. *The American Journal of Occupational Therapy*, 67 (2), pp. 171-176.

Timans, R., Wouters, P. & Heilbron, J. (2019) 'Mixed methods research: what it is and what it could be'. *Theory and Society*, 48 (2), pp. 193-216.

Tollman, S. M., Bastian, H., Doll, R., Hirsch, L. J. & Guess, H. A. (2001) 'What are the effects of the fifth revision of the Declaration of Helsinki?'. *British Medical Journal*, 323 (7326), pp. 1417-1423.

Treasure, T. & MacRae, K. D. (1998) 'Minimisation: the platinum standard for trials?'. *British Medical Journal*, 317 (7155), pp. 362-363.

Treweek, S., Lockhart, P., Pitkethly, M., Cook, J. A., Kjeldstrøm, M., Johansen, M., Taskila, T. K., Sullivan, F. M., Wilson, S., Jackson, C., Jones, R. & Mitchell, E. D. (2013) 'Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis'. *BMJ Open*, 3 (2), pp. e002360.

Treweek, S., Pitkethly, M., Cook, J., Fraser, C., Mitchell, E., Sullivan, F., Jackson, C., Taskila, T. K. & Gardner, H. (2018) 'Strategies to improve recruitment to randomised trials'. *Cochrane Database of Systematic Reviews*, 2 p. Mr000013 DOI: 10.1002/14651858.MR000013.pub6 (Accessed: Feb 22).

Tsung, B. Y. S., Zhang, M., Mak, A. F. T. & Wong, M. W. N. (2004) 'Effectiveness of insoles on plantar pressure redistribution'. *Journal of rehabilitation research and development*, 41 (6A), pp. 767-774.

Tuttle, L. J., Bittel, D. C., Bittel, A. J. & Sinacore, D. R. (2018) 'Early-Onset Physical Frailty in Adults With Diabesity and Peripheral Neuropathy'. *Canadian Journal of Diabetes*, 42 (5), pp. 478-483.

Uccioli, L., Faglia, E., Monticone, G., Favales, F., Durola, L., Aldeghi, A., Quarantiello, A., Calia, P. & Menzinger, G. (1995) 'Manufactured shoes in the prevention of diabetic foot ulcers'. *Diabetes Care*, 18 (10), pp. 1376-1378.

Ulbrecht, J. S., Hurley, T., Mauger, D. T. & Cavanagh, P. R. (2014) 'Prevention of recurrent foot ulcers with plantar pressure–based in-shoe orthoses: the CareFUL prevention multicenter randomized controlled trial'. *Diabetes Care*, 37 (7), pp. 1982-1989.

Urry, S. (1999) 'Plantar pressure-measurement sensors'. *Measurement Science and Technology*, 10 (1), pp. R16-R32.

Vadiveloo, T., Jeffcoate, W., Donnan, P. T., Colhoun, H. C., McGurnaghan, S., Wild, S., McCrimmon, R. & Leese, G. P. (2018) 'Amputation-free survival in 17,353 people at high risk for foot ulceration in diabetes: a national observational study'. *Diabetologia*, 61 (12), pp. 2590-2597.

Vaismoradi, M., Jones, J., Turunen, H. & Snelgrove, S. (2016) 'Theme development in qualitative content analysis and thematic analysis'. *Journal of Nursing Education and Practice*,

Vaismoradi, M., Turunen, H. & Bondas, T. (2013) 'Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study'. *Nursing & Health Sciences*, 15 (3), pp. 398-405.

van der Ploeg, H. P., Tudor-Locke, C., Marshall, A. L., Craig, C., Hagströmer, M., Sjöström, M. & Bauman, A. (2010) 'Reliability and validity of the international physical activity questionnaire for assessing walking'. *Research Quarterly for Exercise & Sport*, 81 (1), pp. 97-101.

van Deursen, R. (2004) 'Mechanical loading and off-loading of the plantar surface of the diabetic foot'. *Clinical Infectious Diseases*, 39 (Supplement 2), pp. S87-S91.

van Netten, J. J., Bus, S. A., Apelqvist, J., Lipsky, B. A., Hinchliffe, R. J., Game, F., Rayman, G., Lazzarini, P. A., Forsythe, R. O., Peters, E. J. G., Senneville, É., Vas, P., Monteiro-Soares, M. & Schaper, N. C. (2020a) 'Definitions and criteria for diabetic foot disease'. *Diabetes/metabolism research and reviews*, 36 (S1), p. e3268 DOI: 10.1002/dmrr.3268 [Online]. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/dmrr.3268.

van Netten, J. J., Jannink, M. J., Hijmans, J. M., Geertzen, J. H. & Postema, K. (2010) 'Use and usability of custom-made orthopedic shoes'. *Journal of rehabilitation research and development*, 47 (1), pp. 73-81.

van Netten, J. J., Price, P. E., Lavery, L. A., Monteiro-Soares, M., Rasmussen, A., Jubiz, Y. & Bus, S. A. (2016) 'Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review'. *Diabetes/metabolism research and reviews*, 32 Suppl 1 pp. 84-98.

van Netten, J. J., Raspovic, A., Lavery, L. A., Monteiro-Soares, M., Rasmussen, A., Sacco, I. C. N. & Bus, S. A. (2020b) 'Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review'. *Diabetes/metabolism research and reviews*, 36 (S1), pp. e3270.

Van Spall, H. G., Toren, A., Kiss, A. & Fowler, R. A. (2007) 'Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review'. *JAMA*, 297 (11), pp. 1233-1240.

Vedhara, K., Dawe, K., Wetherell, M. A., Miles, J. N. V., Cullum, N., Dayan, C., Drake, N., Price, P., Tarlton, J., Weinman, J., Day, A. & Campbell, R. (2014) 'Illness beliefs predict self-care behaviours in patients with diabetic foot ulcers: A prospective study'. *Diabetes Research and Clinical Practice*, 106 (1), pp. 67-72.

Vetter, T. R. & Mascha, E. J. (2017) 'Defining the Primary Outcomes and Justifying Secondary Outcomes of a Study: Usually, the Fewer, the Better'. *Anesthesia & Analgesia*, 125 (2), pp. 678-681.

Veves, A., Murray, H. J., Young, M. J. & Boulton, A. J. (1992) 'The risk of foot ulceration in diabetic patients with high foot pressure: a prospective study'. *Diabetologia*, 35 (7), pp. 660-663.

Vik, S. A., Maxwell, C. J. & Hogan, D. B. (2004) 'Measurement, correlates, and health outcomes of medication adherence among seniors'. *Annals of Pharmacotherapy*, 38 (2), pp. 303-312.

Vincent, A. M., Callaghan, B. C., Smith, A. L. & Feldman, E. L. (2011) 'Diabetic neuropathy: cellular mechanisms as therapeutic targets'. *Nature Reviews Neurology*, 7 (10), pp. 573–583.

Viswanathan, V., Madhavan, S., Gnanasundaram, S., Gopalakrishna, G., Nath Das, B., Rajasekar, S. & Ramachandran, A. (2004) 'Effectiveness of Different Types of Footwear Insoles for the Diabetic Neuropathic Foot: A follow-up study'. *Diabetes Care*, 27 (2), pp. 474-477.

Vulcano, E., Tracey, J. A., 3rd & Myerson, M. S. (2016) 'Accurate Measurement of First Metatarsophalangeal Range of Motion in Patients With Hallux Rigidus'. *Foot & Ankle International*, 37 (5), pp. 537-541.

Waaijman, R., Arts, M. L. J., Haspels, R., Busch-Westbroek, T. E., Nollet, F. & Bus, S. A. (2012) 'Pressure-reduction and preservation in custom-made footwear of patients with diabetes and a history of plantar ulceration'. *Diabetic Medicine*, 29 (12), pp. 1542-1549 1548p.

Waaijman, R., Keukenkamp, R., de Haart, M., Polomski, W. P., Nollet, F. & Bus, S. A. (2013) 'Adherence to Wearing Prescription Custom-Made Footwear in Patients With Diabetes at High Risk for Plantar Foot Ulceration'. *Diabetes Care*, 36 (6), pp. 1613-1618.

Wafai, L., Zayegh, A., Woulfe, J., Aziz, S. M. & Begg, R. (2015) 'Identification of Foot Pathologies Based on Plantar Pressure Asymmetry'. *Sensors*, 15 (8), pp. 20392-20408.

Walsh, J., Hoffstad, O., Sullivan, M. & Margolis, D. (2016) 'Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom'. *Diabetic Medicine*, 33 (11), pp. 1493-1498.

Walters, S. J., Bonacho dos Anjos Henriques-Cadby, I., Bortolami, O., Flight, L., Hind, D., Jacques, R. M., Knox, C., Nadin, B., Rothwell, J., Surtees, M. & Julious, S. A. (2017) 'Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme'. *BMJ Open*, 7 (3), p. e015276 DOI: 10.1136/bmjopen-2016-015276 [Online]. Available at: https://bmjopen.bmj.com/content/bmjopen/7/3/e015276.full.pdf.

Warren, G. L., Maher, R. M. & Higbie, E. J. (2004) 'Temporal patterns of plantar pressures and lower-leg muscle activity during walking: effect of speed'. *Gait Posture*, 19 (1), pp. 91-100 DOI: 10.1016/s0966-6362(03)00031-6.

Wearing, S. C., Urry, S., Smeathers, J. E. & Battistutta, D. (1999) 'A comparison of gait initiation and termination methods for obtaining plantar foot pressures'. *Gait Posture*, 10 (3), pp. 255-263.

Weir, J. P. (2005) 'Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM'. *The Journal of Strength & Conditioning Research*, 19 (1), pp. 231-240.

Wells, M., Williams, B., Treweek, S., Coyle, J. & Taylor, J. (2012) 'Intervention description is not enough: evidence from an in-depth multiple case study on the untold role and impact of context in randomised controlled trials of seven complex interventions'. *Trials*, 13 (1), p. 95 DOI: 10.1186/1745-6215-13-95 (Accessed: 2012/06/28).

Wenke, R. J., Ward, E. C., Hickman, I., Hulcombe, J., Phillips, R. & Mickan, S. (2017) 'Allied health research positions: a qualitative evaluation of their impact'. *Health Research Policy and Systems*, 15 (1), p. 6 DOI: 10.1186/s12961-016-0166-4.

Westby, M., Norman, G., Vedhara, K., Game, F. & Cullum, N. (2020) 'Psychosocial and behavioural prognostic factors for diabetic foot ulcer development and healing: a systematic review'. *Diabetic Medicine*, 37 pp. 1244–1255

Wettasinghe, A. H., Dissanayake, D. W. N., Allet, L., Katulanda, P. & Lord, S. R. (2020) 'Sensorimotor impairments, postural instability, and risk of falling in older adults with diabetic peripheral neuropathy'. *International Journal Of Diabetes In Developing Countries*, 40 pp. 547-554.

Whitehead, A. L., Sully, B. G. & Campbell, M. J. (2014) 'Pilot and feasibility studies: is there a difference from each other and from a randomised controlled trial?'. *Contemporary Clinical Trials*, 38 (1), pp. 130-133.

Whiting, L. S. (2008) 'Semi-structured interviews: Guidance for novice researchers'. *Nursing Standard*, 22 (23), pp. 35-40.

Whitley, E. & Ball, J. (2002) 'Statistics review 4: Sample size calculations'. *Critical Care*, 6 (4), p. 335 DOI: 10.1186/cc1521 [Online]. Available at: https://doi.org/10.1186/cc1521 (Accessed: 2002/05/10).

Williams, A. E., Martinez-Santos, A., McAdam, J. & Nester, C. J. (2016) "Trial and error…', '…happy patients' and '…an old toy in the cupboard': a qualitative investigation of factors that influence practitioners in their prescription of foot orthoses'. *Journal of foot and ankle research*, 9 (1), p. 11 DOI: 10.1186/s13047-016-0142-9 (Accessed: 2016/03/22).

Woodburn, J. & Helliwell, P. (1997) 'Observations on the F-Scan in-shoe pressure measuring system'. *Clinical Biomechanics*, 12 (3), p. S16 DOI: 10.1016/s0268-0033(97)88329-5 (Accessed: Apr).

World Health Organisation (2019) *Classification of diabetes mellitus.* Geneva, (Report No. 9241515708). Available at: Licence: CC BY-NC-SA 3.0 IGO (Accessed: 25 July 2020).

Wrobel, J. S., Ammanath, P., Le, T., Luring, C., Wensman, J., Grewal, G. S., Najafi, B. & Pop-Busui, R. (2014) 'A novel shear reduction insole effect on the

thermal response to walking stress, balance, and gait'. *Journal of Diabetes Science and Technology*, 8 (6), pp. 1151-1156 *cmedm* DOI: 10.1177/1932296814546528.

Yavuz, M., Erdemir, A., Botek, G., Hirschman, G. B., Bardsley, L. & Davis, B. L. (2007) 'Peak plantar pressure and shear locations: relevance to diabetic patients'. *Diabetes Care*, 30 (10), pp. 2643-2645.

Yin, R. K. (2015) *Qualitative research from start to finish.* Guilford publications.

Zelik, K. E. & Adamczyk, P. G. (2016) 'A unified perspective on ankle push-off in human walking'. *Journal of Experimental Biology*, 2019 (23), pp. 3676-3683.

Zhang, P., Lu, J., Jing, Y., Tang, S., Zhu, D. & Bi, Y. (2017) 'Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis'. *Annals Of Medicine*, 49 (2), pp. 106-116.

Zimny, S., Schatz, H. & Pfohl, M. (2004) 'The role of limited joint mobility in diabetic patients with an at-risk foot'. *Diabetes Care*, 27 (4), pp. 942-946.

Appendices

Appendix 1 Published study methods protocol

Collings, R., Freeman, J. A., Latour, J., Vickery, P. J., Glasser, S., Lepesis, V., Enki, D. & Paton, J. (2019) 'INSoles To Ease Pressure (INSTEP) Study: a multicentre, randomised controlled feasibility study to compare the effectiveness of a novel instant optimised insole with a standard insole for people with diabetic neuropathy: a study protocol.' *BMJ Open*, 9 (3), p. e029185 DOI: 10.1136/bmjopen-2019-029185 [Online].

BMJ Open

INSoles To Ease Pressure (INSTEP) Study: a multicentre, randomised controlled feasibility study to compare the effectiveness of a novel instant optimised insole with a standard insole for people with diabetic neuropathy: a study protocol

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To cite: Collings R, Freeman JA, Latour J, *et al*. INSoles To Ease Pressure (INSTEP) Study: a multicentre, randomised controlled feasibility study to compare the effectiveness of a novel instant optimised insole with a standard insole for people with diabetic neuropathy: a study protocol. *BMJ Open* 2019;**0**:e029185. doi:10.1136/bmjopen-2019-029185

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-029185).

Received 16 January 2019
Revised 23 January 2019
Accepted 24 January 2019

Check for updates

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ABSTRACT

Introduction Foot ulceration is a multifactorial complication of diabetes. Therapeutic insoles and footwear are frequently used to reduce elevated tissue pressures associated with risk of foot ulceration. A novel protocol using in-shoe pressure measurement technology to provide an instant optimised insole and house shoe solution has been developed, with the aim of reducing foot ulceration.

Aim This study aims to assess the feasibility of conducting a multicentre randomised controlled trial to compare the effectiveness of a novel instant optimised insole with a standard insole for people with diabetic neuropathy.

Methods and analysis This study is a participant and assessor blinded, randomised, multicentre parallel group feasibility trial with embedded qualitative study. Seventy-six participants will be recruited from three podiatry clinics and randomised to an optimised insole plus usual care (intervention group) or standard insole plus usual care (control group) using a minimisation by randomisation procedure by study centre and previous ulcer status. Assessment visits and data collection will be at baseline, 3 months, 6 months and 12 months. Feasibility and acceptability of the trial procedures will be determined in terms of recruitment and retention rates, data completion rates, intervention adherence and effectiveness of the blinding. Assessment of the appropriateness and performance of outcome measures will inform selection of the primary and secondary outcomes and sample size estimate for the anticipated definitive randomised controlled trial. Clinical outcomes include incidence of plantar foot ulceration and change in peak plantar pressure. Twelve participants (four from each centre) and three treating podiatrists (one from each centre) will be interviewed to explore their experiences of receiving and delivering the intervention.

Ethics and dissemination The study was approved by the South-West Exeter Research Ethics Committee. Findings will be disseminated through conference presentations, public platforms and academic publications.

Trials registration number ISRCTN16011830; Pre-results.

Strengths and limitations of this study

- This study assesses the feasibility of undertaking a definitive robustly designed large-scale randomised controlled study.
- This study contributes to the limited literature on feasibility of reducing foot ulceration by insole and footwear provision for those at risk of diabetic foot ulceration.
- Qualitative aspects of this study will help inform future studies to optimise their acceptability to patients.
- The current study is not designed to find differences in outcomes.

INTRODUCTION

Foot ulceration is a devastating multifactorial complication of diabetes. It is expected that 25% of people with diabetes will develop a foot ulcer at some point.[1] Foot ulceration is a limb and life-threatening condition known to precede 80% of all diabetic lower limb amputations.[2]

It is estimated that 30% of people with diabetes have diabetic peripheral neuropathy, a primary risk factor for the development of foot ulceration.[3] The forefoot region is most susceptible to foot ulceration, particularly in neuropathic feet absent of protective sensation, where plantar loads and tissue stress

are increased.[4–6] Therapeutic footwear and insoles are provided to offload and reduce harmful tissue stresses in people with diabetes.[7] Guidelines for foot care for people with diabetes recommend the use of therapeutic footwear and insoles in the preventative management of those at risk of foot ulceration.[8]

The efficacy of offloading the diabetic, neuropathic foot through the use of therapeutic footwear and insoles varies considerably.[7 9–12] This variability may be explained by different study designs, and a lack of consensus in prescriptions for therapeutic footwear and insoles between clinicians, clinics and services which are largely based on expert opinion and clinical experience.[13] There are no studies or protocols to indicate the optimal features or efficiency of the different devices designed to improve outcomes.

The use of an objective approach to guide footwear and insole design to improve clinical outcomes has been suggested. The use of pedobarography to identify vulnerable areas and influence the position and type of footwear and insole modifications may offer a more optimised approach and improve offloading outcomes.[14] Arts *et al*[15] and Waaijman *et al*[16] introduced modifications to therapeutic footwear and insoles guided by in-shoe pressure technology, both noting reductions in peak pressure of 6.7%–24% and 15%–23%, respectively, compared with premodification. Lin *et al*[17] used in-shoe technology to guide the defined removal of 'plugs' at sites of interest out of the insole and achieved 32% peak pressure reduction. However current protocols focus only on altering the distribution of pressure across the weight-bearing foot. As yet, no consideration has been given to the temporal aspect of gait. Specifically, that total contact area between foot to floor (and therefore insole function) is dependent on the phase of gait and gait style.

To our knowledge, this is the first protocol that uses pedobarography to categorise the temporal loading pattern of the foot according to gait style, combined with information from pressure patterns. This information informs the design of insoles to optimally reduce in-shoe pressure through the implementation of a simple standardised algorithm. The insole is manufactured and issued at the same appointment, avoiding detrimental delays. This protocol describes a feasibility study to assess the implementation of a novel insole design algorithm aimed at producing insoles which optimally reduce in-shoe peak pressure and subsequent ulceration risk in people with diabetes and neuropathy. Therefore, the purpose of this study is to assess if a definitive randomised controlled trial (RCT) using a novel protocol is feasible.

Following recommendations from the Consolidated Standards of Reporting Trials (CONSORT) collaboration[18 19] this feasibility trial will allow operational experience to inform the conduct and final design of a definitive trial so that it can be successfully delivered with confidence.

OBJECTIVES

The purpose of this feasibility study is to:

Assess the feasibility and acceptability of the trial procedures comparing the delivery of a novel instant optimised insole with a standard insole for people with diabetic neuropathy.

Select the most appropriate primary outcome measure and secondary outcome measures and inform the sample size calculation of the future RCT.

Explore the experiences of participants receiving optimised instant insoles and Pulman house shoe, or flat-bed cushioned inlay insole and Pulman house shoe, and podiatrists' experiences of delivering the intervention. This information will fine-tune the smooth delivery of the intervention protocol to optimise participant engagement in terms of recruitment, insole and footwear adherence, and minimise loss to follow-up.

METHODS AND ANALYSIS

Trial design/setting

The Insoles to Ease Pressure (INSTEP) Study is a participant and assessor blinded, randomised, multicentre parallel group feasibility trial with an embedded qualitative study. A CONSORT Study flow chart is presented (figure 1) which outlines the flow of participants through the trial. Seventy-six participants will be randomised (allocation ratio 1:1) to receive an optimised insole plus usual care (intervention) or standard insole plus usual care (control). We will generate and implement the minimisation by randomisation procedure through a web-based system. This will ensure equal numbers of participants in the two groups by location, study centres and by previous ulceration status. Intervention group allocation (in a 1:1 ratio) will be revealed to the treatment podiatrist after the collection of baseline data. Insole and footwear will be issued by the same podiatrist immediately after randomisation. The allocated insole will be worn for 12 months. After initial baseline assessment, outcome measures will be attained at 3 months, 6 months and 12 months postrandomisation.

A subsample of 12 trial participants (4 from each centre) and three treating podiatrists (one from each centre) will be purposely selected. Semistructured interviews will be used to qualitatively explore their experiences of receiving/delivering the intervention. In addition, a further six participants will complete a daily journal with a 1-week account of their experiences at 3 months, 6 months and 12 months.

Trial centres are three community hospitals located in the south-west of England: Torbay (Torbay and South Devon NHS Foundation Trust), Exeter (Royal Devon and Exeter Foundation NHS Trust) and Solent (Solent NHS Trust).

Participants and recruitment

People with diabetes and neuropathy will be identified and initially screened for eligibility by the usual podiatry clinical team, while attending for a routine foot care

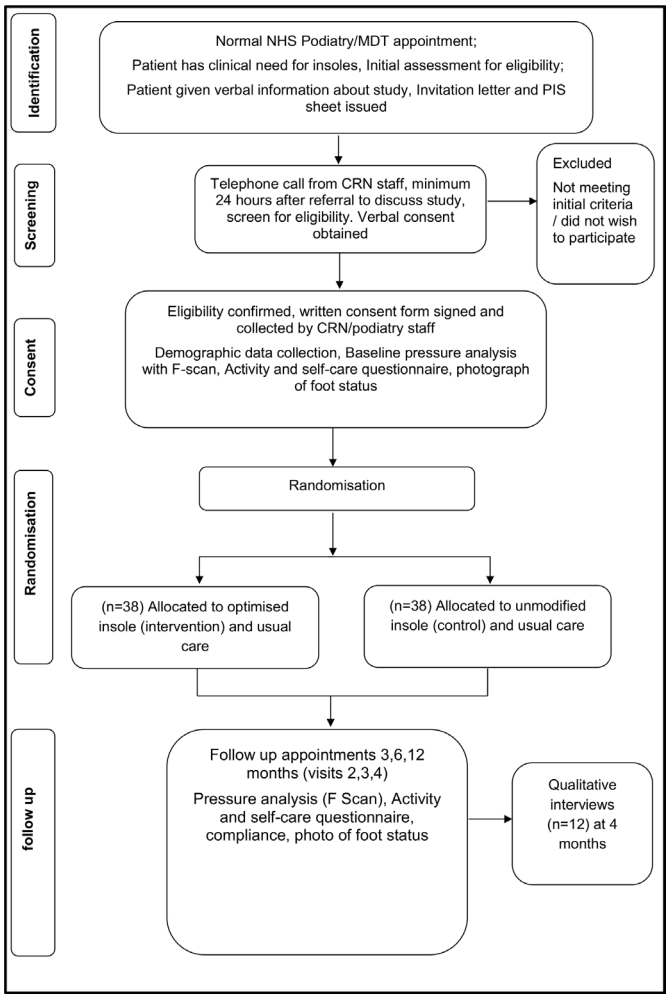

Figure 1 Trial flow chart. MDT, multidisciplinary diabetic team; NHS, National Health Service.

appointment located within the hospital-based multidisciplinary diabetic team foot clinic or podiatry community clinic. The inclusion and exclusion criteria are presented in table 1. Potential participants will be given a brief verbal explanation of the trial by their treating podiatrist and provided with written information. They will have at least 24 hours to review this information and ask any further questions before volunteering to participate. Potential participants will be telephoned to confirm their continued willingness to participate and offered an appointment for baseline measurement. Written informed consent will be obtained by a Good Clinical Practice trained nurse or podiatrist at the baseline visit.

Intervention

Two different insoles will be evaluated for feasibility and acceptability in this trial: instant optimised insole (intervention) and cushioned inlay insole (control). Both insoles will be custom-made to foot size and constructed using materials commonly used in the manufacture of insoles for people with diabetes. Each insole will be fitted into a Pulman house shoe, which will be measured to fit the participants' foot. In addition, both insoles will have an activated data logger (Orthotimer, Algeos, Liverpool, UK) embedded into the insole to measure adherence.

Optimised insole

The instant optimised insole will be designed and optimised using the F-scan in-shoe pressure analysis system (Tekscan, Boston, Massachusetts, USA). A novel algorithm based on walking gait style (Mr Wobbly, Mr Stompee, Mr Propulsive) has been developed. The design and modification(s) will be informed by the treatment algorithm (online supplementary material 1). The optimised insole

Table 1 Insoles to Ease Pressure (INSTEP) Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Confirmed diagnosis of type 1 or type 2 diabetes as confirmed by medical records	Any other significant disease or disorder*
Aged over 18 years	Non-healing foot ulcer at another site that requires targeted offloading
Identified clinical need for offloading insoles by podiatrist	Unable to walk 5 m with/without walking aid
Neuropathic (sensory peripheral diabetic neuropathy defined as insensitivity of a 5.07/10 g monofilament[16])	Unable to stand on either leg independently for 10 s (±chair aid to assist in balance)
Palpable pedal foot pulses	Lacking capacity or unwilling to give consent
Able and willing to comply with all trial requirements	Already wearing existing insoles that are clinically appropriate
	Peripheral vascular disease (non-reconstructible vascular disease as determined by arterial duplex)
	Unwilling to wear therapeutic footwear
	Gross foot deformity, for example, Charcot foot or fixed rear foot deformity
	Unable to provide adequate consent to undertake the trial procedures
	Major amputation of part of the foot

*Which, in the opinion of the principal investigator (PI), may put the participant at risk of health deterioration, such as falls.

Table 2 Study procedures for the Insoles to Ease Pressure (INSTEP) Study

Procedure	Baseline clinic (visit 1)	3 months* follow-up clinic (visit 2)	4 months qualitative follow-up*	6 months* follow-up clinic (visit 3)	12 months* follow-up clinic (visit 4)
Confirmation of eligibility	X				
Informed consent	X				
Demographics and history	X				
Plantar pressure in-shoe recording	X	X		X	X
Randomisation	X				
Intervention provision (including plantar pressure recording)	X				
Outcome measures (ulcer incidence; photographs, activity and self-care questionnaires)	X	X		X	X
Semistructured interviews (in participants' homes)			X		
Journal entries		X		X	X
Serious adverse event recording		X	X	X	X

*Postrandomisation.

will consist of a preconstructed base (slim-flex, full-length, low-density, Shore A30, Algeos, UK). Regions of interest (ROIs) therein may be further formed to accommodate for prominent areas, with the addition of modifications that are designed to offload pressures from bony prominences in specific regions. These will be used to reduce peak plantar pressure values in conjunction with real-time pressure data from the F-scan system in the specific ROIs.

Control insole

The control group will receive a flatbed cushioned inlay insole (3 mm Poron 4000) with 5 mm medium density EVA heel lift cut to shoe size.

Study procedures

An overview of the study procedures are outlined in table 2. All participants will be invited to attend the baseline visit and three further study appointments at 3 months, 6 months and 12 months postrandomisation. Data at all time points will be collected in case report forms (CRFs) by the trial team. All data will be entered into a secure database by the Peninsula Clinical Trials Unit.

Baseline visit (visit 1)

At visit 1, written informed consent will be obtained on arrival. In addition, clinical information will be obtained from the patient and their medical notes including demographics (gender, age, height, weight, smoker/non-smoker, ethnicity), medical history (type 1 or type 2 diabetes, time since diabetes diagnosis, history of previous foot ulceration, current foot ulceration, other medical conditions), blood glycated haemoglobin levels and glomerular filtration rate. This information will be used to account for cofounding variables and analyses of differences and similarities between intervention arm groups.

Data collection

Participants will perform in-shoe measurement tests with the treating podiatrist. The F-Scan in-shoe pressure measurement system (Tekscan, Boston, Massachusetts, USA) is capable of reliable and repeatable data collection.[20–22] The F-scan system sensors are connected to a computer via a cuff unit and a 9.14 m long cable. Data are collected at a sampling rate of 50 Hz for 4 s. The TekScan software identifies pressures from 960 sensing locations on the plantar foot. Plantar pressures can be identified from individual samples or peak pressures can be identified over a total stance phase.

To optimise the accuracy and repeatability of the data collected within this study the following precautions will be incorporated within the data collection protocol. New sensors will be provided for each participant for each individual foot, labelled and used to collect data from that foot throughout the duration of the study. Participants will put on standard socks (20 denier stockings) and will be fitted with a standard house shoe (Markell Shoe Company, Yonkers, New York, USA). Any callus on the foot will be removed prior to fitting the socks and footwear, and prior to any recording.

Using a standardised protocol, participants will then be asked to undertake two test walks between chairs.[23 24] This will allow the determination of usual gait velocity and for acclimatisation of the sensors. Between the chairs a premarked 5 m walkway with a little extra at each end to allow for deceleration and acceleration of gait will be used to determine gait velocity (m/s). This will be calculated by stopwatch recording of the time taken to pass between the marks. The walks will allow for the sensors

to bed in and the temperature to reach equilibrium. Before each data collection session each patient will be weighed and each pair of insoles calibrated against body weight. Following calibration, if sensor saturation pressure exceeds 2000 kPa the sensor will be discarded. Calibration will be checked for within-foot and between-foot repeatability, and if excessive variation of ±10% is observed, the sensor will be recalibrated.

The test will consist of two runs initially. However, extra runs may be required if gait velocity is not consistent (a maximum of 5% deviation will be allowed). From each run, a minimum of three steps per foot is required to be analysed (excluding first and last steps of each run).

Using recorded F-Scan data, a maximum of three 'Regions of Interest' can be identified for each participant, where *ROI=mean peak pressure >350 kPa and/or is a recently healed ulcer site(s) or callus/corn formation*. In addition, identification of type of gait style (Mr Wobbly, Mr Stompee, Mr Propulsive) by analysis of the recorded F-scan pressure time curve and force time curve will occur.

Follow-up visits

Postrandomisation at 3 months (visit 2), 6 months (visit 3) and 12 months (visit 4) will occur. In-shoe pressure measurement testing, described in the baseline visit, will be repeated. Outcome measures will be collected at each visit. Participants who cease involvement in the study prior to the visits will be invited to report the reason. This will be optional.

Outcome measures

Primary outcomes

The primary outcomes include feasibility and acceptability of the INSTEP Study. Quantitative and qualitative feedback will be obtained to identify the main determinants of experience and acceptance of the INSTEP trial, in particular the following measures and operational criteria:

- Assessing numbers of eligible participants from the target population.
- Assessing recruitment and retention rates of eligible participants through the trial.
- Assessing the willingness of participants to be randomised.
- Assessing the pragmatism of delivering the insole intervention in the proposed settings.
- Measuring variation and fidelity in the delivery of the intervention in each group. A fidelity checklist will evaluate the adherence by the treating podiatrists to the standardised protocol of intervention delivery.
- Assessing the completeness of data sets/outcome measures.
- Assessing the success of the blinding.

Secondary outcomes

Anthropometric measurements of height and weight will be attained at baseline. In addition, sensory neuropathy,[25] visual acuity, clinician rated biomechanical foot and ankle status using validated clinical measures (foot posture index FP-6,[26] ankle joint,[27] subtalar joint,[28] first metatarsal phalangeal joint range of motion[29]) and clinician rated balance status (Romberg's test)[30] will be collected.

Clinical outcomes in the form of mean peak plantar pressure at ROI, in the standardised Pulman house shoe and measurements of plantar foot ulceration[31] as measured by photograph following predefined assessment criteria[32] will be assessed at baseline, 3 months, 6 months and 12 months. Adherence to wearing the insole and footwear (Pulman house shoe) as measured by a data logger (Orthotimer, Algeos, Liverpool, UK) will be recorded.

Patient self-reported outcomes will be assessed at baseline, 3 months, 6 months and 12 months. The Nottingham Assessment of Functional Footcare Questionnaire[33] is an instrument that is used in routine care to identify those whose usual foot care might put their feet at risk of future ulceration. The International Physical Activity Questionnaire[34] is an instrument for monitoring of physical activity and inactivity.

Blinding

Every effort will be made to ensure the participants and the assessor (chief investigator) remains blinded to treatment allocation until the end of the study. The chief investigator and the participants will complete a blinding assessment form after each measurement session to evaluate the effectiveness of the blinding. Successful blinding will be assessed using the Blinding Index.[35]

Statistical analysis plan

A comprehensive statistical analysis plan (SAP) will be drafted prior to the final database lock; the SAP will be agreed with the trial steering committee (TSC) in the absence of a data monitoring committee. An extended CONSORT[18] flow chart will be used to present descriptive data on screening, enrolment, intervention allocation, follow-up and assessment. It will also show any deviations from protocol, for example, participants receiving an 'incorrect' treatment. Descriptive data will be presented by the intervention group on baseline characteristics, for example, age, sex, type of diabetes.

Proposed primary outcome analysis

Analyses will summarise the feasibility outcomes: data from screening, recruitment and follow-up logs will be used to generate realistic estimates of eligibility, recruitment, consent and follow-up rates in the trial population. In addition, adherence data (eg, session attendance and insole/footwear adherence) will be used to contribute to the evaluation of the acceptability and concordance to the insole intervention. Completion rates will be estimated for each of the patient-reported and clinical outcome measures at each time point. All such estimates will be accompanied by appropriate CIs, to allow assumptions to be made in the planning of the definitive trial. The baseline characteristics of individuals lost to follow-up will be

compared with those who complete the feasibility trial to identify any potential bias. Means and SDs arising from differences between the intervention and control arms to inform a power calculation for sample size estimate for the main RCT will be made.

Progression to a full trial will occur if the following minimum success criteria are achieved, or if there is reason to believe that suitable enhancements can be made to the full trial to ensure that any concerns are circumvented:

- 70% recruitment of the intended 76 participants within the 13-month recruitment window.
- 75% retention of participants within the 12-month trial period.
- 80% completion rate of primary and secondary outcome measures at baseline, 3 months, 6 months and 12 months.

Proposed secondary outcome analysis

Further analyses will summarise the proposed primary and secondary patient-reported and clinical outcomes at each time point. Descriptive statistics of the proposed primary and secondary outcomes will be produced, as appropriate for each measure for each trial arm. Interval estimates of the potential intervention effects, relative to control only, will be produced in the form of a 95% CIs, to ensure that the effect size subsequently chosen for powering the definitive trial is plausible, but no formal hypothesis testing will be undertaken of the feasibility data.

Qualitative analysis

Thematic analysis will be used for the analysis of the interviews and journals. This method includes a strategy for identifying themes and subthemes.[36] The transcripts of the interviews and journal entries will be uploaded to the qualitative analysis program NVivo. To avoid individual bias, two researchers will independently read and code the transcripts. The codes will be formulated from the text fragments and will possibly be revised during the process of reading the transcripts. The two researchers will then discuss the results of the individual codes and try to reach consensus. After this, the codes will be reviewed and themes will be formulated.

Meaningful text fragments will be determined, as will codes (subthemes) and themes related to the trial objectives. Data extracts will be accompanied by narrative to elaborate why the extract is analytically interesting.

All participants will be anonymised and pseudonyms used to demonstrate different participants' experiences. If any information is disclosed during the trial that could pose a risk of harm to the participant or others, the chief investigator, where appropriate, will report and act accordingly.

Patient involvement

Patients were involved in the design and are currently involved in the conduct of this research. During the planning stage, priority of the research question, choice of outcome measures and methods of recruitment were informed by discussions with patients through a focus group session and two structured interviews. Patients form the membership of the independent TSC and of the trial management group. Once the trial has been published, participants will be informed of the results in a study newsletter suitable for a non-specialist audience.

Data collection and management

Trial data collected at each centre by the research podiatrists and clinical research nurses will be recorded on trial-specific CRFs and will be considered the source data. The data manager will review the data being sent at regular intervals and report back to each centre if there is any discrepancy. The original completed CRF will be checked for completeness to ensure there are no missing items. Data will be entered into the database via a bespoke web-based data entry system encrypted using secure sockets layer (SSL).

Sample size

As this is a feasibility trial the sample size is pragmatic and a power calculation is neither relevant nor possible. In this feasibility trial, while centres are likely to start recruitment in a staggered fashion, our overall target recruitment will be 2 per month per centre up to a total of 76 participants (38 per group). A CI approach has been used to establish feasible adherence rates. Based on an estimated completion rate of 75%, at least 75 patients are required. This is based on obtaining a 95% CI for a single proportion with a specified lower bound of the CI of 0.70 and a marginal error of 0.05. Data collected on proposed secondary outcomes will provide data on which sample size calculations can be performed in the future RCT.

Adverse events

Adverse events (AEs) are, according to the definitions, any unfavourable or unintended event affecting patients in the study. In cases of prolongation of hospitalisation, death or significant clinical sequelae, these events are defined as serious AEs (SAEs), the occurrence of which will be informed to the study sponsor and the TSC at short notice. During protocol treatment, all deaths, all SAEs that are life-threatening and any unexpected SAE must be reported to the chief investigator using the SAE form within 48 hours of the initial observation of the event. In this trial, only those non-serious AEs associated with the lower limb, foot and mobility need to be reported. Safety aspects of the study will be monitored by the TSC, which will receive unblinded data for its judgement.

To standardise and optimise implementation of the intervention, and to further ensure the safety and well-being of research participants, all participants will be provided with standardised information on footwear and insole usage, how to increase wear time of the insoles, foot self-inspection and what to do in the event of a 'foot attack'. This information will be reiterated at each

appointment by the treating podiatrist. Participants will be advised to contact the treating podiatrist should any problems occur, in order that they can advise remanagement of these issues.

Ethical issues

The protocol, V.1.0 (12/7/2017), was reviewed by the South-West Exeter Research Ethics Committee (REC) and was given a favourable opinion (REC ref 17/SW/0169) on 18 September 2017. Health Research Authority regulatory approval was given on 19 September 2017 and the study was adopted on the NIHR portfolio on 15 August 2017. Plymouth University is the sponsor of the study. The study will comply with the International Conference for Harmonisation of Good Clinical Practice guidelines and the UK Framework for Health and Social Care Research

Amendments to the protocol or study documents will be submitted to the REC and can only be implemented once approval has been obtained. Amendments will be tracked in the protocol and the version of the protocol will be updated.

Dissemination plan and impact

It is the intention that the results of this study will be published in peer-reviewed journals and presented at national and international conferences. Authorship will be determined per internationally agreed criteria for authorship. Participant-level data will be available following publication of results on request. Results will be disseminated to the patient and public community via social media, newsletter articles and presentations at patient conferences and forums, led by the patient partners.

DISCUSSION

The proposed study will allow for all information collected providing important parameters to consider running a large-scale RCT and to identify potential constraints and possible solutions.

Current trends in the provision of insoles and therapeutic footwear are diverse for people with diabetes and neuropathy at risk of foot ulceration.[37] A scarcity of evidence base for the appropriate design, modification and manufacture results in a lack of clear guidance for clinicians. As healthcare systems are also moving towards personalised medicine, the use of an in-shoe pressure measurement system and insole paradigm that will guide and personalise insoles and therapeutic footwear with no manufacturing delays has been developed.

The main limitations of the study are those characteristic of feasibility studies, the lack of power to present a statistically significant difference in outcomes. It may have a high dropout rate, so predictors of discontinuation should be assessed comparing characteristics of compliant patients with those who were lost to follow-up.

However, and despite the aforementioned limitations, the findings and outputs from the proposed feasibility study will take us closer to designing a future cost-effective trial in people with diabetes and neuropathy at risk of foot ulceration.

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Funding R. Collings is funded by a National Institute for Health Research (NIHR) Clinical Doctoral Research Fellowship (ICA-CDRF-2015-01-054) for this research project."

Disclaimer The content presents independent research funded by NIHR. The views expressed are those of the author(s) and not necessarily those of the National Health Service (NHS), the NIHR or the Department of Health and Social Care.

Competing interests None declared.

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Data sharing statement The data set and data analysis will be available upon request from the corresponding author.

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REFERENCES

1. Carls GS, Gibson TB, Driver VR, *et al*. The economic value of specialized lower-extremity medical care by podiatric physicians in the treatment of diabetic foot ulcers. *J Am Podiatr Med Assoc* 2011;101:93–115.
2. Driver VR, Fabbi M, Lavery LA, *et al*. The costs of diabetic foot: the economic case for the limb salvage team. *J Am Podiatr Med Assoc* 2010;100:335–41.
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4. Tong JWK, Ng EYK. Preliminary investigation on the reduction of plantar loading pressure with different insole materials (SRP – Slow Recovery Poron®, P – Poron®, PPF – Poron®+Plastazote, firm and PPS – Poron®+Plastazote, soft). *Foot* 2010;20:1–6.
5. Fernando ME, Crowther RG, Pappas E, *et al*. Plantar pressure in diabetic peripheral neuropathy patients with active foot ulceration, previous ulceration and no history of ulceration: a meta-analysis of observational studies. *PLoS One* 2014;9:e99050.
6. Armstrong DG, Peters EJ, Athanasiou KA, *et al*. Is there a critical level of plantar foot pressure to identify patients at risk for neuropathic foot ulceration? *J Foot Ankle Surg* 1998;37:303–7.
7. Paton J, Bruce G, Jones R, *et al*. Effectiveness of insoles used for the prevention of ulceration in the neuropathic diabetic foot: a systematic review. *J Diabetes Complications* 2011;25:52–62.
8. National Institute for Health and Care Excellence. Diabetic Foot problems: prevention and management. (NICE Guideline 19). 2018 https://www.nice.org.uk/guidance/ng19 (Accessed 15 Oct 2018).

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REFERENCES

1. Carls GS, Gibson TB, Driver VR, *et al*. The economic value of specialized lower-extremity medical care by podiatric physicians in the treatment of diabetic foot ulcers. *J Am Podiatr Med Assoc* 2011;101:93–115.
2. Driver VR, Fabbi M, Lavery LA, *et al*. The costs of diabetic foot: the economic case for the limb salvage team. *J Am Podiatr Med Assoc* 2010;100:335–41.
3. Van Dieren S, Beulens JW, van der S, *et al*. The global burden of diabetes and its complications: an emerging pandemic. *Eur J Cardiovasc Prev Rehabil rehabilitation* 2010;17:s3–8.
4. Tong JWK, Ng EYK. Preliminary investigation on the reduction of plantar loading pressure with different insole materials (SRP – Slow Recovery Poron®, P – Poron®, PPF – Poron®+Plastazote, firm and PPS – Poron®+Plastazote, soft). *Foot* 2010;20:1–6.
5. Fernando ME, Crowther RG, Pappas E, *et al*. Plantar pressure in diabetic peripheral neuropathy patients with active foot ulceration, previous ulceration and no history of ulceration: a meta-analysis of observational studies. *PLoS One* 2014;9:e99050.
6. Armstrong DG, Peters EJ, Athanasiou KA, *et al*. Is there a critical level of plantar foot pressure to identify patients at risk for neuropathic foot ulceration? *J Foot Ankle Surg* 1998;37:303–7.
7. Paton J, Bruce G, Jones R, *et al*. Effectiveness of insoles used for the prevention of ulceration in the neuropathic diabetic foot: a systematic review. *J Diabetes Complications* 2011;25:52–62.
8. National Institute for Health and Care Excellence. Diabetic Foot problems: prevention and management. (NICE Guideline 19). 2018 https://www.nice.org.uk/guidance/ng19 (Accessed 15 Oct 2018).

9. Bus SA, Valk GD, van Deursen RW, *et al*. The effectiveness of footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in diabetes: a systematic review. *Diabetes Metab Res Rev* 2008;24(Suppl 1):S162–S180.
10. Heuch L, Tyndall J, Cook-Johnson R, *et al*. The effectiveness of methods of off-loading to prevent diabetic foot ulcers in adults with diabetes: A Systematic Review. *JBI Libr Syst Rev* 2012;10(56 Suppl):1–14.
11. Bus SA, van Deursen RW, Armstrong DG, *et al*. Footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in patients with diabetes: a systematic review. *Diabetes Metab Res Rev* 2016;32(Suppl 1):99–118.
12. van Netten JJ, Price PE, Lavery LA, *et al*. Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review. *Diabetes Metab Res Rev* 2016;32(Suppl 1):84–98.
13. Nester CJ, Graham A, Martinez-Santos A, *et al*. National profile of foot orthotic provision in the United Kingdom, part 1: practitioners and scope of practice. *J Foot Ankle Res* 2017;10:35.
14. Bus SA, Haspels R, Busch-Westbroek TE. Evaluation and optimization of therapeutic footwear for neuropathic diabetic foot patients using in-shoe plantar pressure analysis. *Diabetes Care* 2011;34:1595–600.
15. Arts ML, Waaijman R, de Haart M, *et al*. Offloading effect of therapeutic footwear in patients with diabetic neuropathy at high risk for plantar foot ulceration. *Diabet Med* 2012;29:1534–41.
16. Waaijman R, Arts ML, Haspels R, *et al*. Pressure-reduction and preservation in custom-made footwear of patients with diabetes and a history of plantar ulceration. *Diabet Med* 2012;29:1542–9.
17. Lin TL, Sheen HM, Chung CT, *et al*. The effect of removing plugs and adding arch support to foam based insoles on plantar pressures in people with diabetic peripheral neuropathy. *J Foot Ankle Res* 2013;6:29.
18. Eldridge SM, Chan CL, Campbell MJ, *et al*. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ* 2016;355:i5239.
19. Chan AW, Tetzlaff JM, Altman DG, *et al*. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
20. Hsiao H, Guan J, Weatherly M. Accuracy and precision of two in-shoe pressure measurement systems. *Ergonomics* 2002:45:537–55.
21. Ahroni JH, Boyko EJ, Forsberg R. Reliability of F-scan in-shoe measurements of plantar pressure. *Foot Ankle Int* 1998;19:668–73.
22. Mueller MJ, Strube MJ. Generalizability of in-shoe peak pressure measures using the F-scan system. *Clin Biomech* 1996:11:159–64.
23. Mueller MJ, Hastings M, Commean PK, *et al*. Forefoot structural predictors of plantar pressures during walking in people with diabetes and peripheral neuropathy. *J Biomech* 2003;36:1009–17.
24. Mueller MJ, Minor SD, Sahrmann SA, *et al*. Differences in the gait characteristics of patients with diabetes and peripheral neuropathy compared with age-matched controls. *Phys Ther* 1994;74:299–308.
25. Feng Y, Schlösser FJ, Sumpio BE. The Semmes Weinstein monofilament examination as a screening tool for diabetic peripheral neuropathy. *J Vasc Surg* 2009;50:675–82.
26. Keenan A-M, Redmond AC, Horton M, *et al*. The foot posture index: rasch analysis of a novel, foot-specific outcome measure. *Arch Phys Med Rehabil* 2007;88:88–93.
27. Bennell KL, Talbot RC, Wajswelner H, *et al*. Intra-rater and inter-rater reliability of a weight-bearing lunge measure of ankle dorsiflexion. *Aust J Physiother* 1998;44:175–80.
28. Elveru RA, Rothstein JM, Lamb RL, *et al*. Methods for taking subtalar joint measurements. *Phys Ther* 1998;68:5:678–82.
29. Vulcano E, Tracey JA, Myerson MS. Accurate measurement of first metatarsophalangeal range of motion in patients with hallux rigidus. *Foot Ankle Int* 2016;37:537–41.
30. Khasnis A, Gokula RM. "Romberg's test.". *J Postgrad Med* 2003;49:2:169.
31. Oyibo SO, Jude EB, Tarawneh I, *et al*. A comparison of two diabetic foot ulcer classification systems: the Wagner and the University of Texas wound classification systems. *Diabetes Care* 2001;24:84–8.
32. Hazenberg CE, van Baal JG, Manning E, *et al*. The validity and reliability of diagnosing foot ulcers and pre-ulcerative lesions in diabetes using advanced digital photography. *Diabetes Technol Ther* 2010;12:1011–7.
33. Booth M. International physical activity questionnaire. Assessment of physical activity: an international perspective. *Res Q Exerc Sport* 2000;71:s114–20.
34. Lincoln N. *Nottingham assessment of functional footcare*: University of Nottingham, 2015.
35. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials* 2004;25:143–56.
36. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006;3:77–101.
37. Chevalier TL, Chockalingam N. Effects of foot orthoses: how important is the practitioner? *Gait Posture* 2012;35:383–8.

Appendix 2 Research ethics committee letter of approval

South West - Exeter Research Ethics Committee
Whitefriars
Level 3
Block B
Lewins Mead
Bristol
BS1 2NT

Study title:	**A multicentre, randomised controlled feasibility study to compare the effectiveness of a novel instant optimised insole with a standard insole for people with diabetic neuropathy.**
REC reference:	**17/SW/0169**
Protocol number:	**FHHS-224903-RC-022**
IRAS project ID:	**224903**

Thank you for your letter of 6th September, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [covering letter]		13 July 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance certificate]		01 August 2016
GP/consultant information sheets or letters	1.0	29 May 2017
Interview schedules or topic guides for participants [interview guide podiatrists]	1.0	07 August 2017
Interview schedules or topic guides for participants [interview guide participants]	1.0	20 August 2017
IRAS Application Form [IRAS_Form_17072017]		17 July 2017
IRAS Checklist XML [Checklist_07092017]		07 September 2017
Other [annual insurance renewal]		
Other [Insole leaflet instruction]	1.0	10 July 2017
Other [Response cover letter]		23 August 2017
Other [response letter2]		06 September 2017
Participant consent form [consent form tracked]	1.1	21 August 2017
Participant consent form [consent form pod tracked]	1.1	06 September 2017
Participant consent form [consent form interviews tracked]	1.1	14 August 2017
Participant information sheet (PIS) [PIS tracked changes]	1.1	21 August 2017
Participant information sheet (PIS) [PIS overall trial]	1.1	21 August 2017
Participant information sheet (PIS) [Podiatrist PIS]	1.0	14 August 2017
Participant information sheet (PIS) [PIS participant interviews]	1.1	14 August 2017
Participant information sheet (PIS) [PIS parti interviews tracked]	1.1	14 August 2017
Referee's report or other scientific critique report [NIHR panel report]		21 November 2016
Referee's report or other scientific critique report [Expert commentator report]		10 April 2017
Research protocol or project proposal [Protocol]	1.0	12 July 2017
Sample diary card/patient card [Participant journal]	1.0	12 July 2017
Summary CV for Chief Investigator (CI)		12 July 2017
Summary CV for supervisor (student research) [CV Joanne Paton]		13 July 2017
Summary CV for supervisor (student research) [CV JM Latour]		12 July 2017
Summary CV for supervisor (student research) [CV Jenny Freeman]		14 July 2017
Summary, synopsis or diagram (flowchart) of protocol in non technical language [participant flow charts]	1.0	12 July 2017
Validated questionnaire	1.0	12 July 2017
Validated questionnaire [questionnaire booklet]	1.1	14 August 2017

17/SW/0169	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Dr Denise Sheehan Chair

Email:nrescommittee.southwest-exeter@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Ms Pam Baxter*

Dr Fiona Roberts, Torbay and Southern Devon NHS Foundation Trust

Appendix 3 HRA letter of approval

Health Research Authority

Mr Richard Collings
NIHR Clinical Doctoral Researcher
Email: hra.approval@nhs.net

University of Plymouth
Peninsula Allied Health Centre
Derriford Road
Plymouth
PL6 8BH

19 September 2017
Dear Mr Collings

Letter of HRA ApprovalStudy title:	**A multicentre, randomised controlled feasibility study to compare the effectiveness of a novel instant optimised insole with a standard insole for people with diabetic neuropathy.**
IRAS project ID:	**224903**
Protocol number:	**FHHS-224903-RC-022**
REC reference:	**17/SW/0169**
Sponsor	**University of Plymouth**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Your IRAS project ID is **224903**. Please quote this on all correspondence.

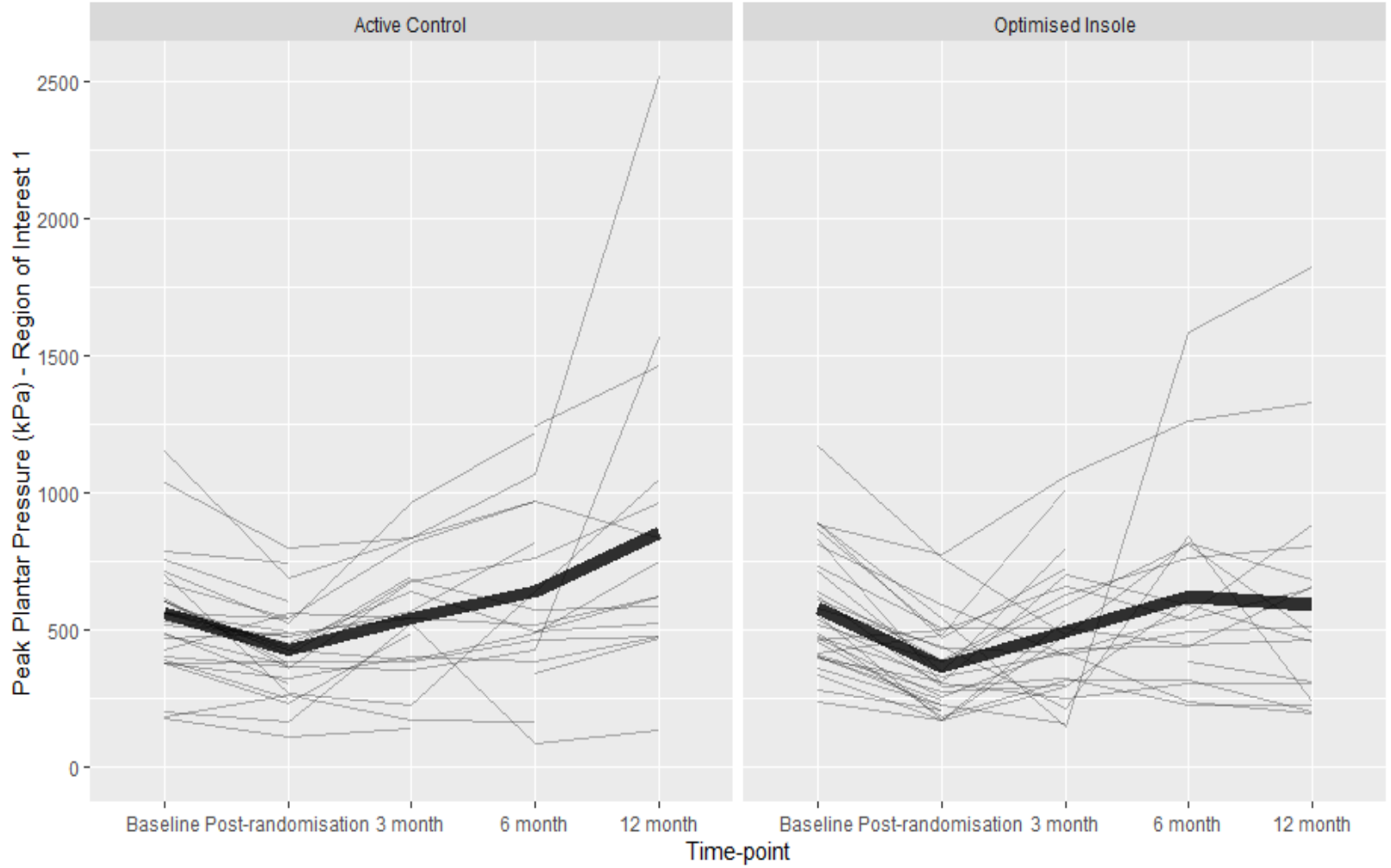
Yours sincerely

Maeve Ip Groot Bluemink
Assessor

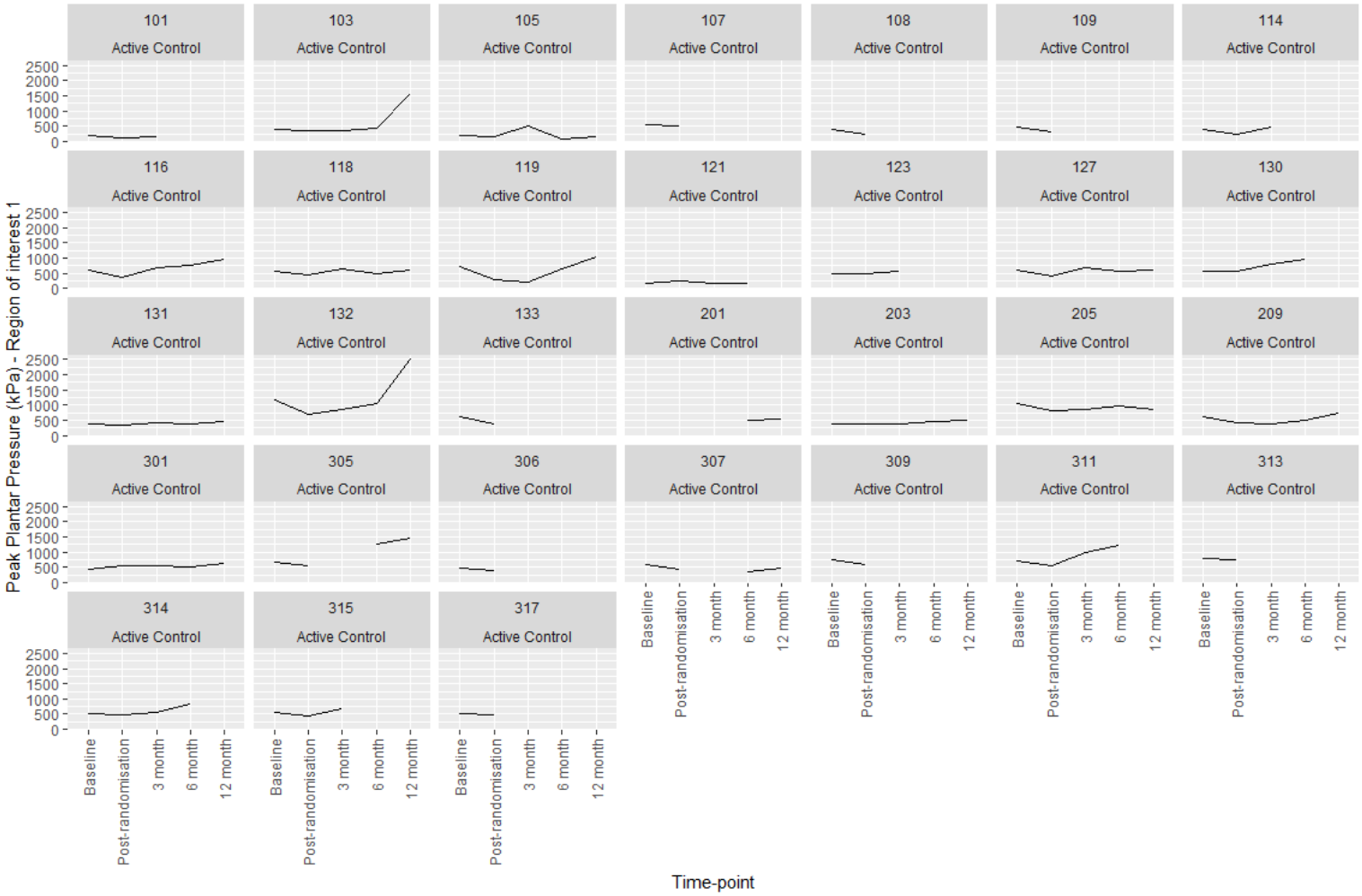
Email: hra.approval@nhs.net

Copy to: Ms Pam Baxter, University of Plymouth – Sponsor Contact
Dr Fiona Roberts, Torbay and Southern Devon NHS Foundation Trust – Lead R&D Contact

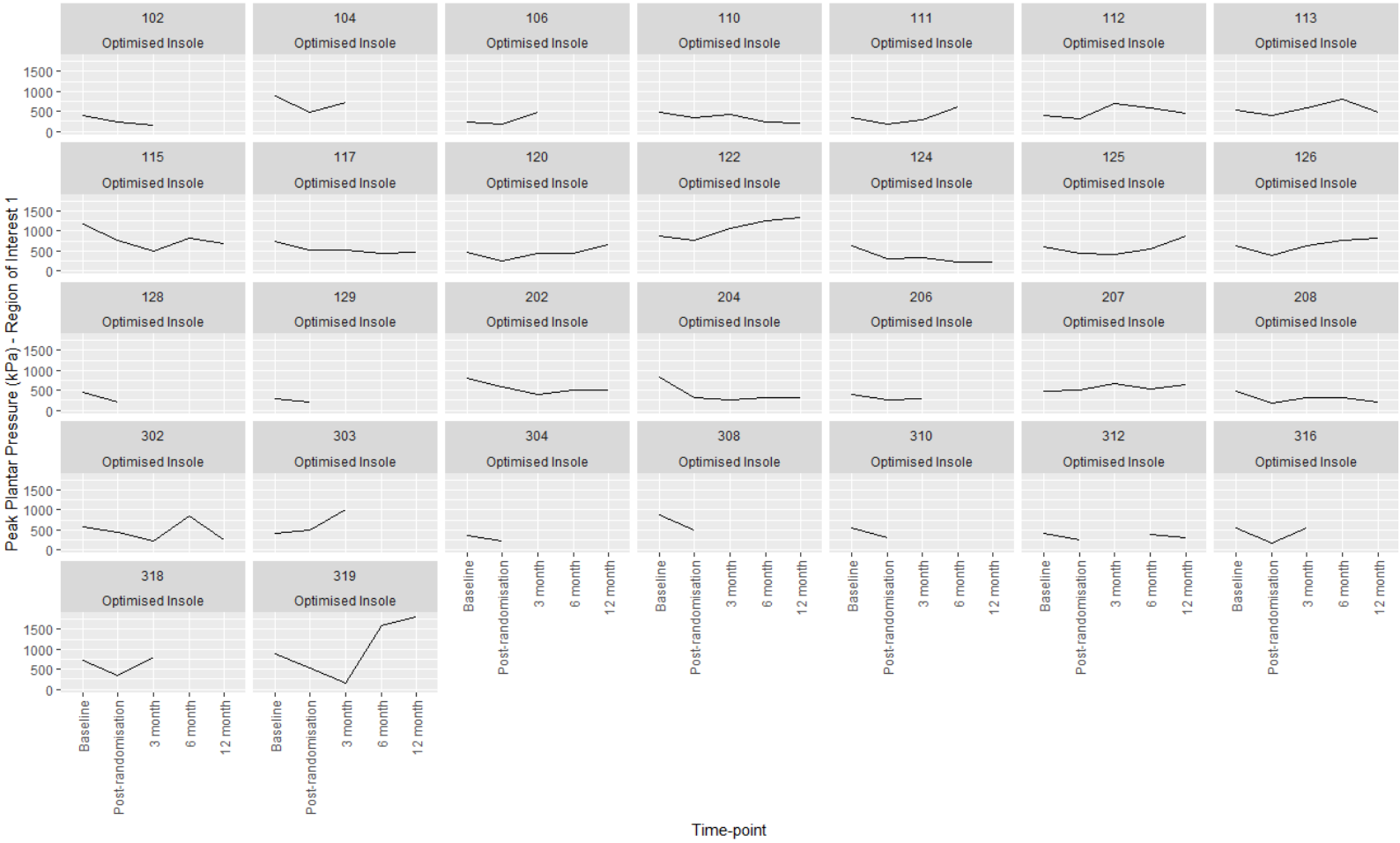
Appendix 4 Mean peak plantar pressure for region of interest-1 by treatment group allocation for time point



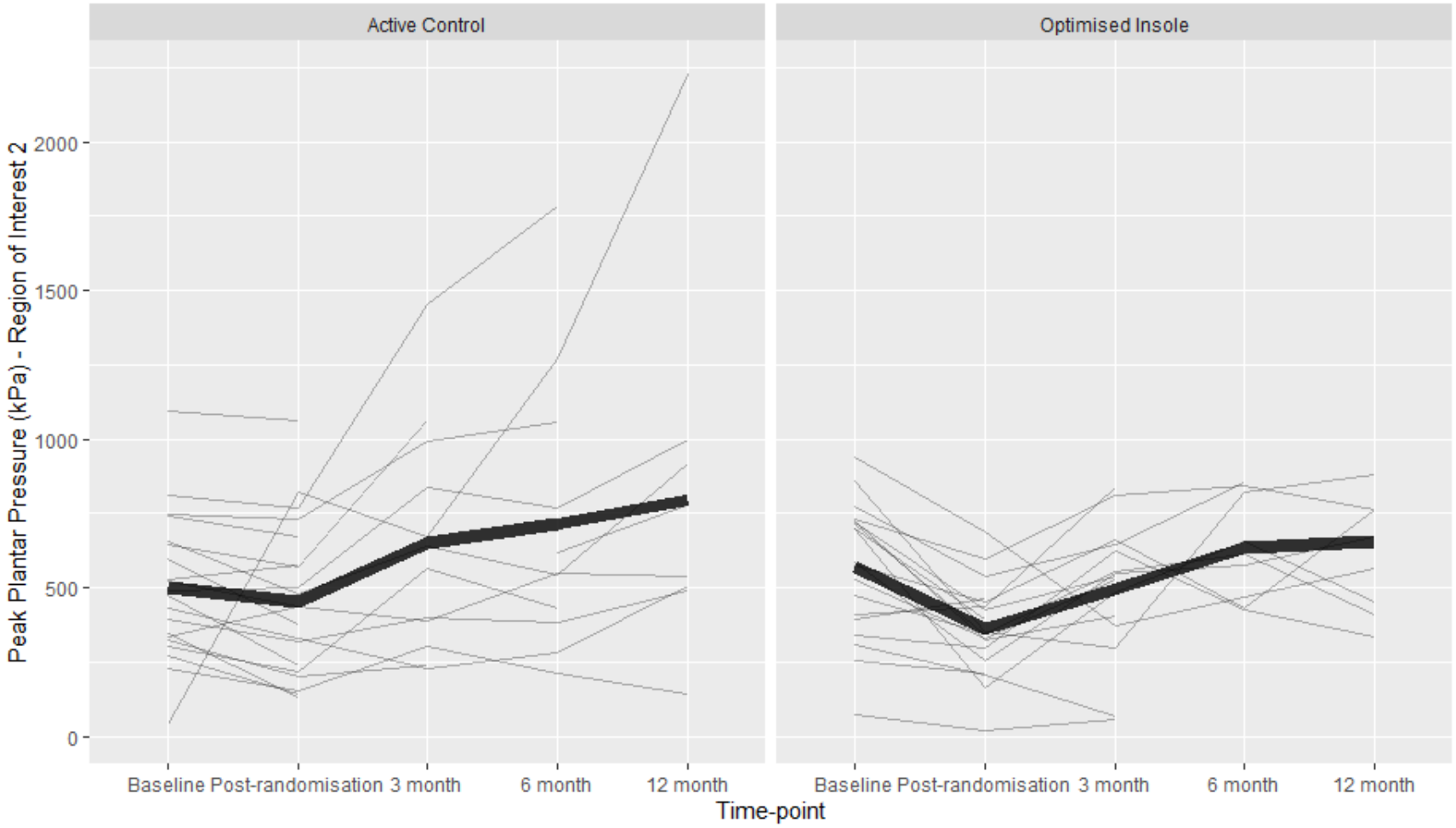
Appendix 5 Mean peak plantar pressure for region of interest-1 by time point for active control insole group for all participants



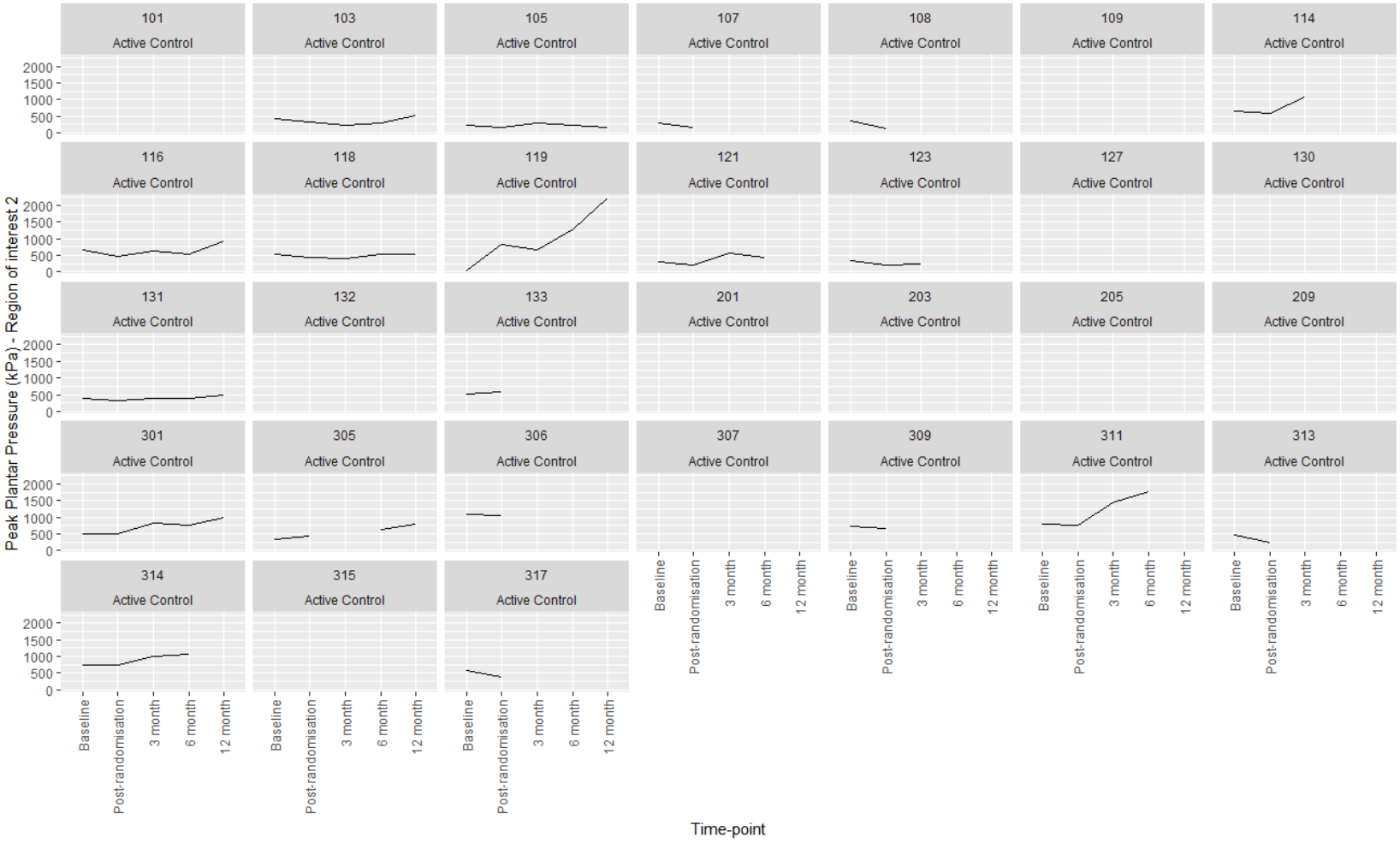
Appendix 6 Mean peak plantar pressure for region of interest-1 by time point for optimised insole group for all participants



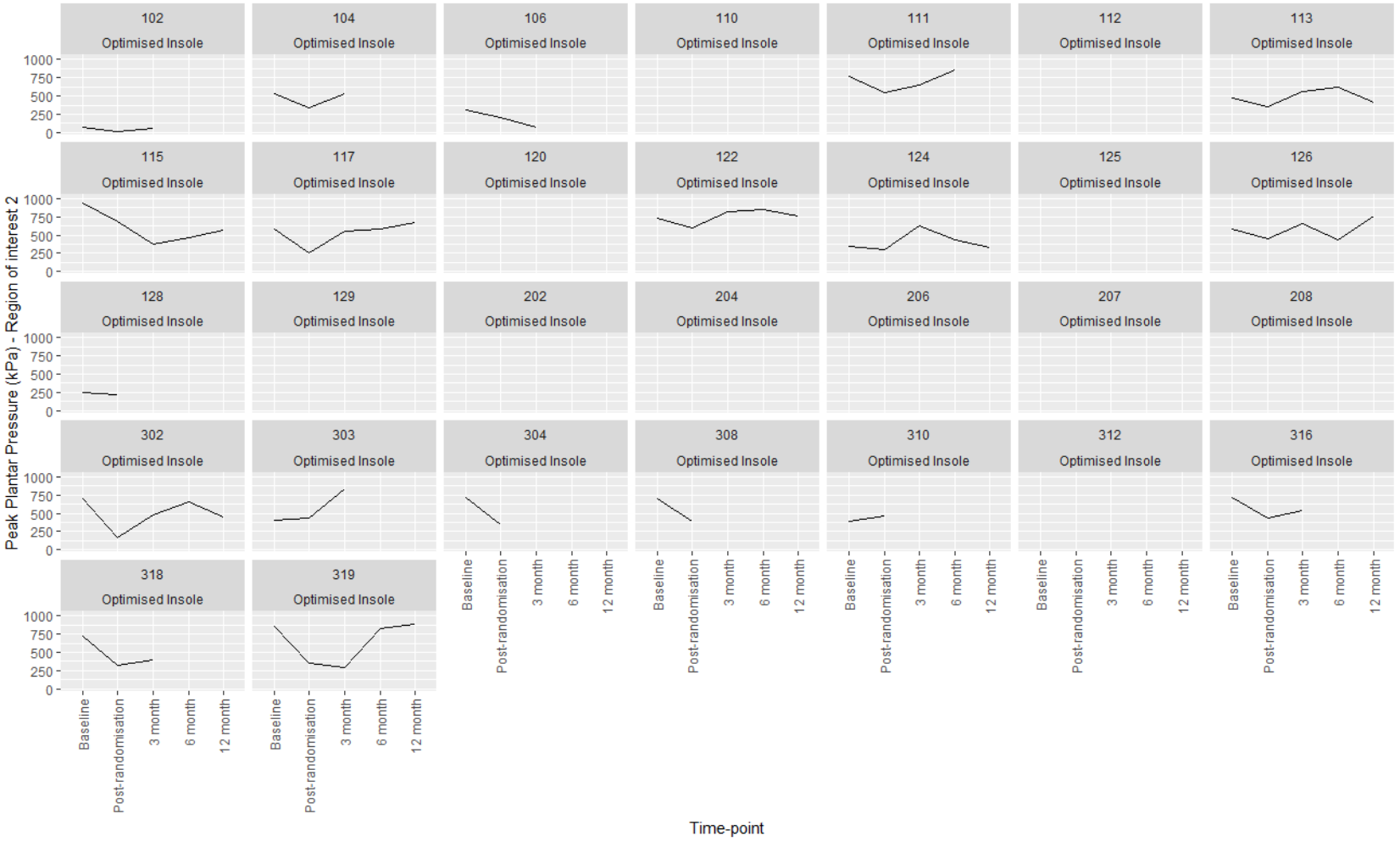
Appendix 7 Mean peak plantar pressure for region of interest-2 by treatment group allocation for time point



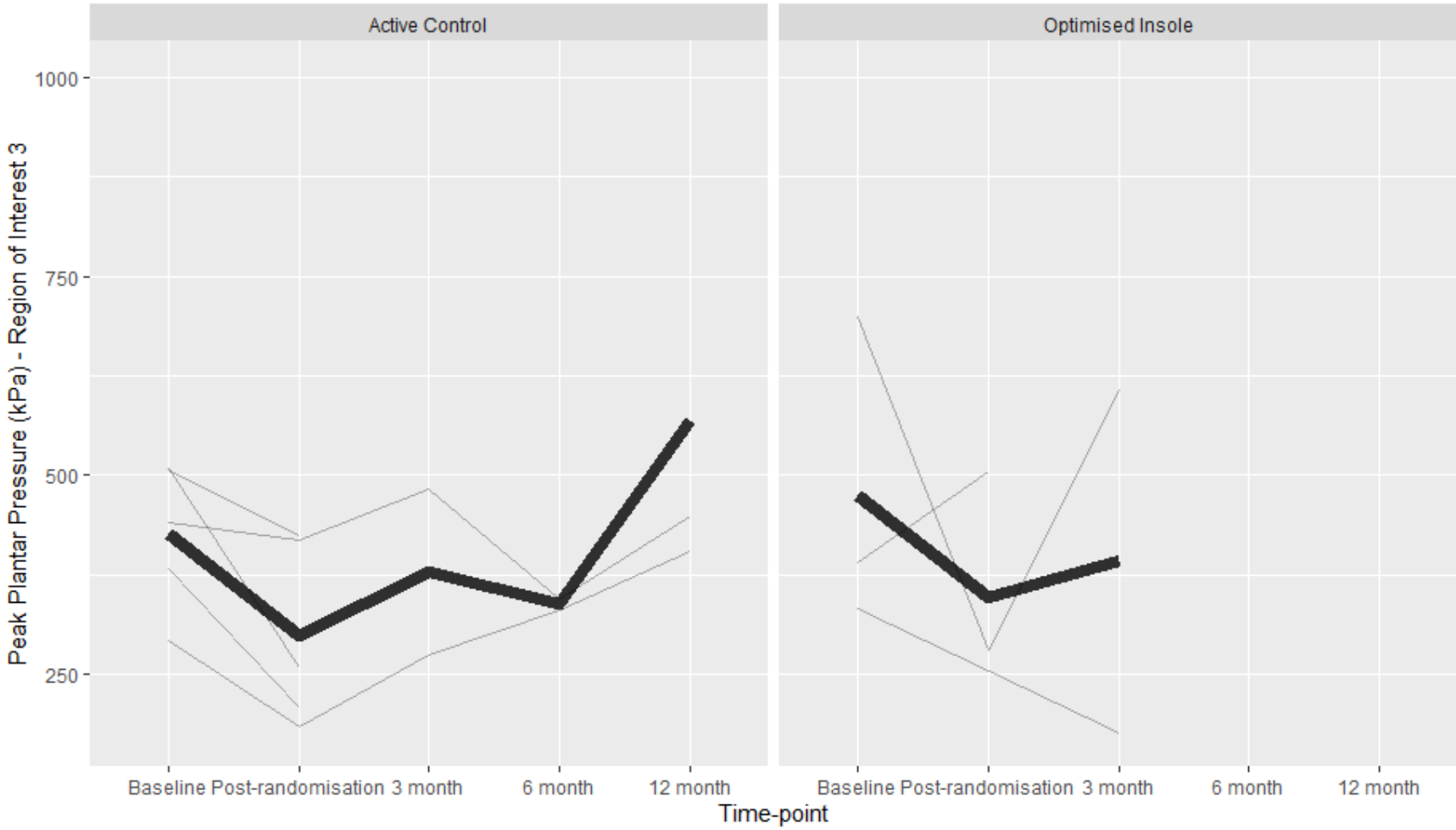
Appendix 8 Mean peak plantar pressure for region of interest-2 by time point for active control insole group for all participants



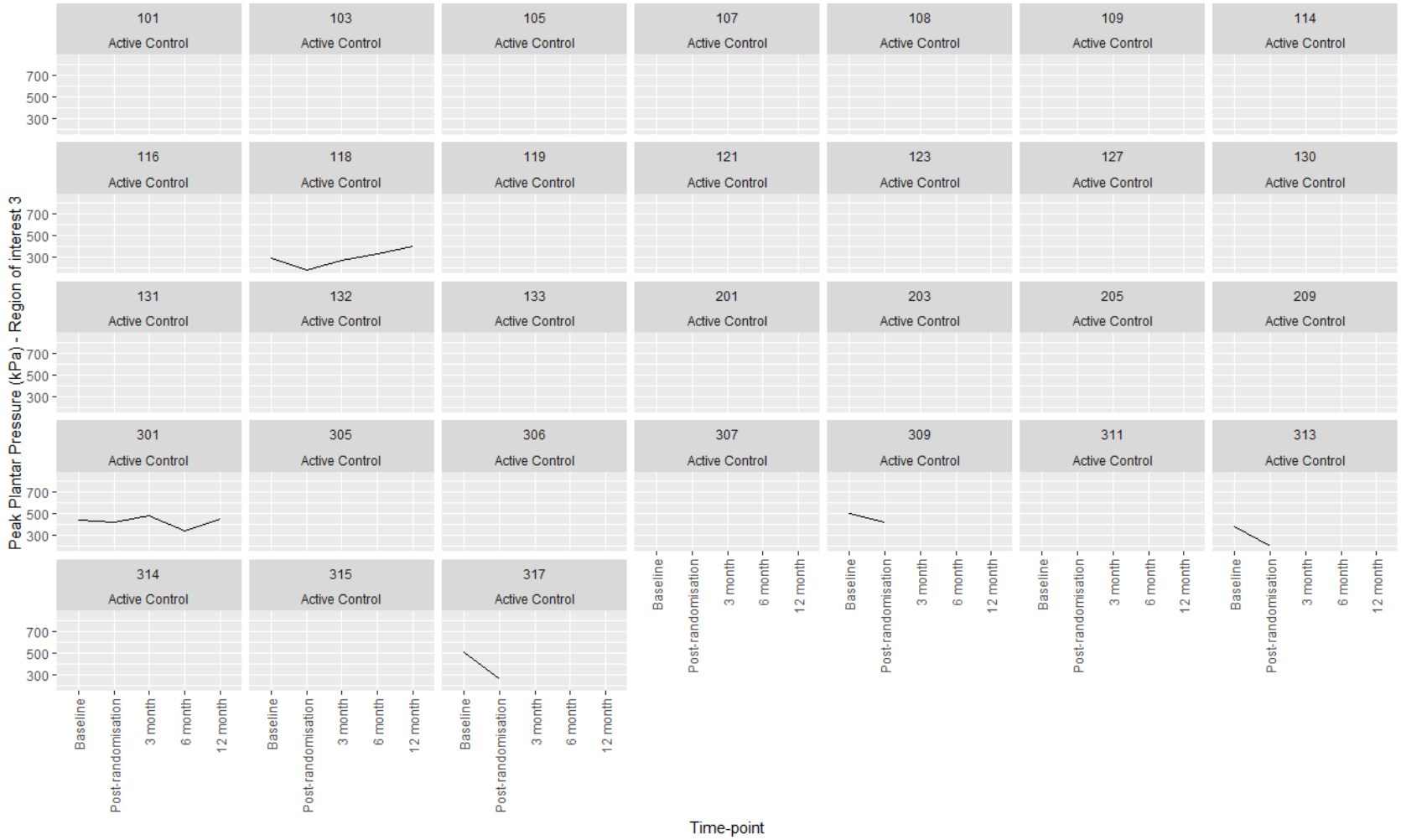
Appendix 9 Mean peak plantar pressure for region of interest-2 by time point for optimised insole group for all participants



Appendix 10 Mean peak plantar pressure for region of interest-3 by time point by treatment group allocation



Appendix 11 Mean peak plantar pressure for region of interest-3 by time point for active control insole group for all participants



Appendix 12 Mean peak plantar pressure for region of interest-3 by time point for optimised insole group for all participants

Appendix 13 Correlations between baseline and follow up measures of plantar pressure for ROI-1