


# BMJ Open Duration of antibiotherapy for patients with diabetic foot osteomyelitis without amputation: a protocol for a systematic review and network meta-analysis

Jing Hu,<sup>1</sup> Zhijun Yu,<sup>2</sup> Haiying Deng,<sup>2</sup> Yajun Chen,<sup>2</sup> Zhenyu Jiang <sup>2</sup>

**To cite:** Hu J, Yu Z, Deng H, *et al.* Duration of antibiotherapy for patients with diabetic foot osteomyelitis without amputation: a protocol for a systematic review and network meta-analysis. *BMJ Open* 2025;**15**:e093342. doi:10.1136/bmjopen-2024-093342

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<https://doi.org/10.1136/bmjopen-2024-093342>).

Received 05 September 2024  
Accepted 02 May 2025



© Author(s) (or their employer(s)) 2025. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ Group.

<sup>1</sup>Department of Endocrinology, Geriatric Hospital Affiliated to Wuhan University of Science and Technology, Wuhan University of Science and Technology, Wuhan, Hubei, China

<sup>2</sup>Institute of Pharmaceutical Process, Hubei Province Key Laboratory of Occupational Hazard Identification and Control, School of Medicine, Wuhan University of Science and Technology, Wuhan, Hubei, China

## Correspondence to

Ms Jing Hu;  
741882453@qq.com and  
Zhenyu Jiang;  
jiangzhenyu@wust.edu.cn

## ABSTRACT

**Introduction** Diabetic foot osteomyelitis (DFO) poses a serious threat to the quality of life and survival of patients, and systemic antibiotic therapy is effective and plays a pivotal role in the management of patients with DFO without amputation. However, the optimal duration of systemic antibiotic therapy is not clear. We aim to perform a network meta-analysis (NMA) to assess the efficacy and safety of different durations of antibiotic therapy for patients with DFO without amputation.

**Methods and analysis** We will search multiple databases, including the China National Knowledge Infrastructure, VIP database, Wanfang Data, ScienceDirect, EBSCO, EMBASE, Web of Science, Cochrane Library, and PubMed. The outcome indicators are remission rate, time needed for complete wound healing, major amputation rates and the rate of antibiotic-related adverse events. Risk of bias will be evaluated using the Cochrane risk-of-bias tool. NMA will be performed using STATA/MP V.15.0. The surface under the cumulative ranking area will be calculated to rank each treatment.

**Ethics and dissemination** This study is a systematic review protocol collecting data from published literature and does not require approval from an institutional review board. Results from this systematic review will be published in a peer-reviewed journal.

**PROSPERO registration number** CRD42023486089.

## INTRODUCTION

Diabetes mellitus is increasingly prevalent around the globe. The global diabetes prevalence in 2021 was estimated to be 10.5% (536.6 million people), rising to 12.2% (783.2 million) in 2045.<sup>1</sup> The lifetime incidence of foot ulcers has previously been estimated to be 19%–34% among persons with diabetes, and more than half of diabetic foot ulcers become infected.<sup>2</sup> About 20% of infected ulcers will spread to the bone, causing diabetic foot osteomyelitis (DFO), which will increase mortality, risk of amputation and healthcare expenditure.<sup>3 4</sup> There is no doubt that DFO has posed a tremendous threat to individual health and society.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This systematic review will evaluate all available evidence from randomised controlled trials (RCTs) to determine the optimal duration of systemic antibiotic therapy for DFO without amputation.
- ⇒ Adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for network meta-analyses (NMA) will strengthen the methodological rigour of this study.
- ⇒ Data will be analysed using pairwise meta-analysis and NMA that will give insights into the comparative efficacy and safety of interventions across the included studies.
- ⇒ The confidence of evidence for the outcomes will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach.
- ⇒ We anticipate that not all the included studies have reported all the outcomes of interest in this review, and the number of RCTs available in some comparisons may be relatively small.

Currently, DFO is primarily treated with systemic antibiotics and may require limb amputation to control the infection in extreme cases. However, amputation leads to a permanent disability, which can significantly reduce the quality of life of patients.<sup>5</sup> Fortunately, it was found that systemic antibiotic therapy has demonstrated reliable therapeutic effects in patients with DFO and could avoid a major amputation.<sup>6 7</sup> The renewed : IWGDF, International Working Group on the Diabetic Foot/Infectious Diseases Society of America (IWGDF/IDSA) guidelines recommend that empirical systemic antibiotic therapy should be started as early as possible in order to control the infection and could be switched to targeted antibiotherapy based on bacterial culture and susceptibility test results.<sup>8</sup> Many clinicians treat DFOs with systemic antibiotic therapy for more than 6 weeks or even months with the intention of improving

therapeutic outcomes,<sup>9 10</sup> despite the recommendation of the guidelines to limit it to 6 weeks.<sup>8</sup> However, long-term administration of antibacterial agents contributes to a rise in antimicrobial resistance and adverse drug reactions, which may make the treatment of DFO more difficult. Studies have revealed that, for DFO without amputation, shorter systemic antibiotic therapy did not increase the risk of clinical or microbiological failure,<sup>11</sup> remission rates were similar between 6-week and 12-week duration systemic antibiotic therapy,<sup>12</sup> and a systemic antibiotic therapy course of 3 weeks resulted in similar remission rates and adverse events to a course of 6 weeks.<sup>13</sup> Nevertheless, the small sample size of these studies limited their results. Thus, it is not known whether the duration can be shortened to 3 weeks. There is currently insufficient evidence to determine the ideal duration of systemic antibiotic therapy for DFO without amputation.

The network meta-analysis (NMA), an extension of pairwise meta-analysis (PMA), combines direct and indirect comparisons to compare and rank various interventions. In this study, we will conduct both PMA and NMA to compare and rank the efficacy and safety of different durations of systemic antibiotic therapy for patients with DFO without amputation to evaluate the most suitable duration of systemic antibiotic therapy. The results of this study will offer valuable evidence to inform recommendations for DFO therapy.

## METHODS

The study protocol was registered in PROSPERO (CRD42023486089). This manuscript was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P) statement<sup>14</sup> (see online supplemental table S1).

### Criteria for inclusion and exclusion

#### Participants

Participants must meet the following inclusion criteria: (1) Age  $\geq 18$  years; (2) Diagnosed with diabetes mellitus; (3) Diagnosed with DFO. DFO diagnosis is confirmed when at least two out of the following three criteria are satisfied: positive microbiological evidence, histological confirmation and radiological indications of bone involvement. The exclusion criteria encompass the following: Participants required amputation due to severe periosteoarticular damage when DFO was diagnosed.<sup>8 15</sup>

#### Interventions

Patients in the experimental group should be treated with systemic antibiotic therapy, which may be administered via injection or oral route. In the absence of definitive culture and susceptibility test results, empirical antibiotic treatment can be administered. However, antibiotics adapted to culture results should be initiated as soon as the results of the tests are definitive. Patients may have undergone appropriate debridement of non-viable infected soft tissues and bones, off-loading and

arterial revascularisation if clinically indicated. The therapeutic interventions that incorporate amputation surgery (including both minor amputation and major amputation) will be excluded.

### Controls

The control group should have followed the same regime as the intervention group with the sole exception of the duration of antibiotherapy.

### Outcomes measures

To be included, studies must have reported at least one of the outcome indicators, such as remission rate which is defined as the percentage of patients achieving remission from DFO at the end of follow-up, the time needed for complete wound healing defined as complete epithelialisation of the wound, major amputation rates which is defined as the percentage of patients who required and underwent major amputation during follow-up, and the rate of antibiotic-related adverse events.

Remission is characterised by: (1) The absence of recurrent, persistent, or new infections at the original site, confirmed by the stabilisation or improvement of radiographic abnormalities on plain X-rays and the absence of local or systemic infection signs at the conclusion of follow-up; and (2) The absence of necessity for surgical intervention or amputation at the initial site by the end of follow-up. According to the guidelines,<sup>8 15</sup> following antibiotic treatment, surgical consultation should be sought in cases of exacerbations, such as more severe infection or DFO complicated by extensive gangrene, necrotising infection, signs suggesting deep (below the fascia) abscess, compartment syndrome, or severe lower limb ischaemia.

### Study type

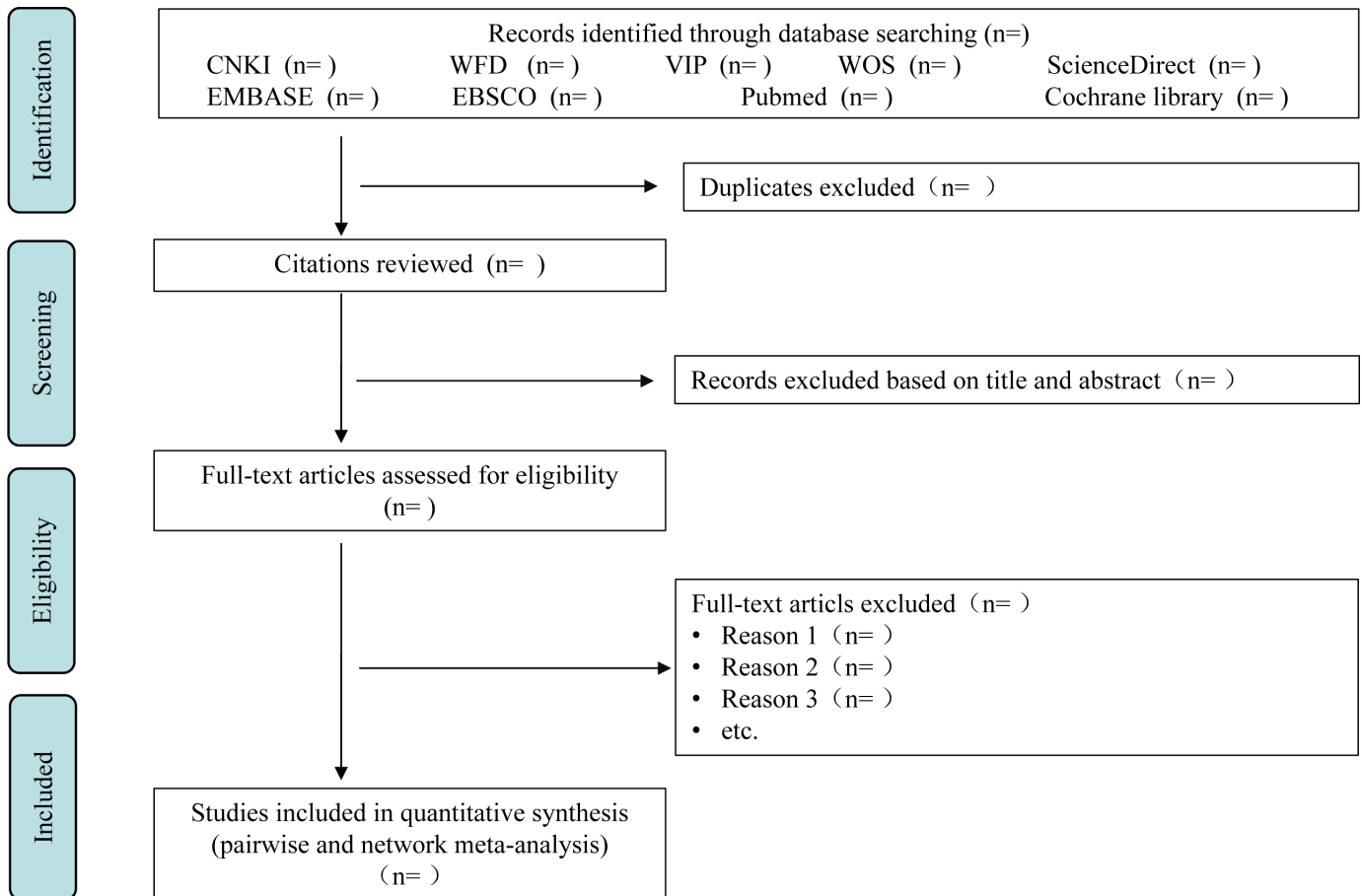
Only randomised controlled trials (RCTs) will be considered for inclusion. Observational studies, case series, qualitative and laboratory studies, and uncontrolled trials will be excluded.

### Literature searches

We will conduct a comprehensive search of relevant publications up to 1 January 2027 in Chinese-language and English-language databases such as the China National Knowledge Infrastructure, VIP database, Wanfang Data, ScienceDirect, EBSCO, Excerpta Medica Database (EMBASE), Web of Science, Cochrane Library, and PubMed. Our search strategy will be tailored for each database, using a combination of MeSH, title, abstract, keywords or free-text words. The retrieval terms include diabetic foot, osteomyelitis, antibacterial agents, bacteriocidal agents, bactericide(s) and antibiotic(s). The search strategy is available in online supplemental table S2. All the records will be concurrently collected and processed in NoteExpress software.

### Study selection

Two researchers will import the retrieved literature into NoteExpress, and duplicates will be removed. They will



**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the study. CNKI, China National Knowledge Infrastructure database; WFD, Wanfang Data; VIP, VIP database; WOS, web of science.

independently read the titles and abstracts for initial screening, and then assess the full texts of all relevant studies according to our inclusion and exclusion criteria. The number of included and excluded studies and reasons for study exclusion will be recorded. If multiple reports of the same study exist, the RCT with the richest baseline and outcome data will be included. Disagreements will be resolved through discussions with a third researcher. As shown in [figure 1](#), the screening and selection process will be presented in a PRISMA flow chart.

### Data extraction

Two researchers will independently extract data using a preset data extraction form. Disagreements will be resolved through discussions with a third researcher. The following data will be extracted: (1) General information (name of the first author, year of publication, study site); (2) Baseline characteristics of participants (sample size, age, sex, diagnosis, location of osteomyelitis, wound score or surface at admission, and microbiology of bone sample cultures); (3) Interventions and controls: (medication, dose, route, duration); (4) Outcome indicator data and quality of the RCTs.

### Assessment of risk of bias in included studies

The risk of bias in the included studies will be evaluated using the Cochrane risk-of-bias tool,<sup>16 17</sup> including the adequate method for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The possible risk-of-bias judgments are as follows: (1) Low risk of bias; (2) Some concerns for bias; and (3) High risk of bias. Two researchers will independently assess the risk of bias, and any disagreement will be resolved by discussion with a third researcher.

### Data analysis plan

We plan to perform a PMA and NMA for every outcome indicator. However, it has to be noted that the findings will be summarised and discussed if a quantitative synthesis is not appropriate.

### Pairwise meta-analysis

PMA will be conducted using RevMan V.5.3 software to compare two interventions at a time. Continuous variables will be analysed using mean difference (MD) with 95% CIs. Relative risk (RR) with 95% CI will be calculated for the dichotomous outcomes. Using the  $I^2$  statistic,

we will evaluate the heterogeneity between the included studies. Substantial heterogeneity, defined as  $I^2$  statistics exceeding 50%, will prompt the utilisation of the random-effects model for PMA, while the fixed-effects model will be employed in other instances. In case of significant heterogeneity, sensitivity analyses will be performed by excluding the studies with potential clinical heterogeneity or likely bias based on the Cochrane risk-of-bias tool.

### Network meta-analysis

NMA will be conducted using the network package in STATA/MP V.15.0, where continuous variables will be analysed using MD with 95% CIs, and RR with 95% CI will be calculated for the dichotomous outcomes. The surface under the cumulative ranking area will be calculated to rank each treatment.<sup>18</sup> Cluster analysis will be used to evaluate the effectiveness and safety of the interventions and determine the optimal duration of antibiotherapy.

Network plots will be constructed to visualise the comparisons. The size of each node will be determined by the number of subjects participating in that intervention. Connecting lines will be thicker if there are more studies included.<sup>18</sup> In the case of closed loops in the intervention structure, it is necessary to assess the inconsistency of the evidence.<sup>19</sup>

In the NMA, uncertainty in effect size estimates will be assessed using 95% predictive intervals (95% PIs), which account for heterogeneity. Uncertainty stemming from heterogeneity will be characterised by discrepancies between the 95% CIs and their corresponding 95% PIs.<sup>18–20</sup> In instances of substantial heterogeneity, sensitivity analyses will be performed by excluding the studies with potential clinical heterogeneity or which are likely to be biased based on the Cochrane risk-of-bias tool. We will evaluate transitivity by assessing the distributions of potential effect modifiers across comparisons. These effect modifiers encompass the following items: age, sex, location of osteomyelitis, wound score or surface at admission, microbiology of bone sample cultures, and the selection of the antimicrobial agent and their administration route. Additionally, publication bias will be evaluated using a funnel plot, in which a symmetrical funnel indicates little bias.

### Certainty of the evidence

Grading of Recommendations Assessment, Development, and Evaluation will be used to assess the confidence of evidence for the outcomes of NMA.<sup>21–23</sup> The certainty of the NMA estimates will be rated as 'high', 'moderate', 'low' or 'very low' based on considerations of risk of bias, inconsistency, indirectness, imprecision and publication bias.

### Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

## DISCUSSION

DFO, one of the severe complications of diabetic foot disease, poses a serious threat to the life and health of patients. Bone and/or joint resection may be required to treat DFO successfully.<sup>8–15</sup> However, patients with DFO are often reluctant to undergo amputation,<sup>24</sup> because maintaining limb function is critical for maintaining independence and quality of life. In addition, systemic antibiotic therapy is successful in a large proportion of patients with DFO without amputation.<sup>25</sup> Thus, a conservative approach with limited resection and without amputation should be chosen if possible. In this study, the NMA approach facilitates the incorporation of both direct and indirect evidence, enabling comparisons of the efficacy and safety of different durations of systemic antibiotic therapy for DFO without amputation. The results of this study will provide insights towards optimising clinical decision-making strategies.

However, it is essential to recognise the potential limitations of this study. First, it was known that factors such as wound surface at admission,<sup>25</sup> locations of osteomyelitis,<sup>26</sup> microbiology of bone sample cultures, the types of wounds (including neuropathic, ischaemic and neuroischaemic types),<sup>27</sup> with or without chronic kidney disease,<sup>28</sup> and the choice of antimicrobial drugs<sup>29</sup> could be identified as the effect modifiers, which could lead to potential heterogeneity. Therefore, there is a need to carefully analyse and discuss before conclusions. Second, the limited number of included studies and small sample sizes may introduce bias in the research results. Thus, subsequent research should perform three crucial assumptions, including heterogeneity, transitivity and consistency, to achieve valid results. Moreover, to ensure the reliability and objectivity of our research conclusions, the search scope should be expanded by reading the retrieved studies and their references, and eligible RCTs should be retrieved as comprehensively as possible.

**Contributors** JH and ZJ conceptualised and designed this protocol of network meta-analysis. ZJ and ZY developed and ran the search strategy. HD and YC developed the initial data extraction template. JH and ZJ were the major contributors in writing the draft of this protocol. All authors reviewed and revised the manuscript, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work. JH is the guarantor.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.



**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

# ORCID iD

Zhenyu Jiang <http://orcid.org/0000-0002-3362-6697>

# REFERENCES

- 1 Sun H, Saeedi P, Karuranga S, *et al*. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract* 2022;183:109119.
- 2 Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. *N Engl J Med* 2017;376:2367–75.
- 3 Ricci L, Scatena A, Tacconi D, *et al*. All-cause and cardiovascular mortality in a consecutive series of patients with diabetic foot osteomyelitis. *Diabetes Res Clin Pract* 2017;131:12–7.
- 4 Geraghty T, LaPorta G. Current health and economic burden of chronic diabetic osteomyelitis. *Expert Rev Pharmacoecon Outcomes Res* 2019;19:279–86.
- 5 Sinha R, van den Heuvel WJA, Arokiasamy P. Factors affecting quality of life in lower limb amputees. *Prosthet Orthot Int* 2011;35:90–6.
- 6 Lipsky BA. Treating Diabetic Foot Osteomyelitis Primarily With Surgery or Antibiotics: Have We Answered the Question? *Diabetes Care* 2014;37:593–5.
- 7 Lesens O, Desbiez F, Theis C, *et al*. Staphylococcus aureus-Related Diabetic Osteomyelitis: Medical or Surgical Management? A French and Spanish Retrospective Cohort. *Int J Low Extrem Wounds* 2015;14:284–90.
- 8 Senneville É, Albalawi Z, van Asten SA, *et al*. IWGDF/IDSA guidelines on the diagnosis and treatment of diabetes-related foot infections (IWGDF/IDSA 2023). *Diabetes Metabolism Res* 2024;40:e3687.
- 9 Arias M, Hassan-Reshat S, Newsholme W. Retrospective analysis of diabetic foot osteomyelitis management and outcome at a tertiary care hospital in the UK. *PLoS ONE* 2019;14:e0216701.
- 10 Commons RJ, Raby E, Athan E, *et al*. Managing diabetic foot infections: a survey of Australasian infectious diseases clinicians. *J Foot Ankle Res* 2018;11:13.
- 11 Haug F, Waibel FWA, Lisy M, *et al*. The impact of the length of total and intravenous systemic antibiotic therapy for the remission of diabetic foot infections. *Int J Infect Dis* 2022;120:179–86.
- 12 Tone A, Nguyen S, Devemy F, *et al*. Six-week versus twelve-week antibiotic therapy for nonsurgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study. *Diabetes Care* 2015;38:302–7.
- 13 Gariani K, Pham T-T, Kressmann B, *et al*. Three Weeks Versus Six Weeks of Antibiotic Therapy for Diabetic Foot Osteomyelitis: A Prospective, Randomized, Noninferiority Pilot Trial. *Clin Infect Dis* 2021;73:e1539–45.
- 14 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
- 15 Gu YQ. Chinese guidelines for diagnosis and treatment of diabetic foot. *Chinese Journal for Clinicians* 2020;48:19–27.
- 16 Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
- 17 Higgins JP, Altman DG, Gøtzsche PC, *et al*. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- 18 Chaimani A, Higgins JPT, Mavridis D, *et al*. Graphical tools for network meta-analysis in STATA. *PLoS ONE* 2013;8:e76654.
- 19 Higgins JPT, Jackson D, Barrett JK, *et al*. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012;3:98–110.
- 20 Int'Hout J, Ioannidis JPA, Rovers MM, *et al*. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open* 2016;6:e010247.
- 21 Salanti G, Del Giovane C, Chaimani A, *et al*. Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 2014;9:e99682.
- 22 Brignardello-Petersen R, Bonner A, Alexander PE, *et al*. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *J Clin Epidemiol* 2018;93:36–44.
- 23 Grade handbook. Available: <https://gdt.gradepro.org/app/handbook/handbook.html> [Accessed 02 Feb 2024].
- 24 Zhou S, Schmidt BM, Henig O, *et al*. Deferring Amputation in Diabetic Foot Osteomyelitis: Doing More Harm Than Good? *Open Forum Infect Dis* 2021;8:ofab184.
- 25 Jordano-Montañez Q, Muñoz-Tatay M, Viadé-Julíà J, *et al*. Diabetic foot osteomyelitis: is conservative treatment possible? *Enferm Infecc Microbiol Clin* 2014;32:555–9.
- 26 Aragón-Sánchez J, Lázaro-Martínez JL, Alvaro-Afonso FJ, *et al*. Conservative Surgery of Diabetic Forefoot Osteomyelitis: How Can I Operate on This Patient Without Amputation? *Int J Low Extrem Wounds* 2015;14:108–31.
- 27 Yotsu RR, Pham NM, Oe M, *et al*. Comparison of characteristics and healing course of diabetic foot ulcers by etiological classification: neuropathic, ischemic, and neuro-ischemic type. *J Diabetes Complications* 2014;28:528–35.
- 28 Zhang J, Chen D, Li X, *et al*. The association between estimated glomerular filtration rate and prognosis in patients with diabetic foot osteomyelitis. *Int Wound J* 2022;19:1650–7.
- 29 Wilson BM, Bessesen MT, Doros G, *et al*. Adjunctive Rifampin Therapy For Diabetic Foot Osteomyelitis in the Veterans Health Administration. *JAMA Netw Open* 2019;2:e1916003.