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Lower-limb neuromuscular electrical stimulation (NMES) for people with chronic kidney disease undergoing dialysis (Protocol)

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[Intervention Protocol]

Lower-limb neuromuscular electrical stimulation (NMES) for people with chronic kidney disease undergoing dialysis

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of neuromuscular electrical stimulation (NMES) on muscle structure and function in people undergoing dialysis.

BACKGROUND

Description of the condition

Chronic kidney disease (CKD) is defined by a glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2 for at least three months, irrespective of cause [1, 2]. It affects approximately 9.1% of the global population [3], and progresses through five stages based on declining GFR [2]. While early stages (1to 3) are often asymptomatic, advanced stages may require dialysis while awaiting transplantation. Dialysis options include haemodialysis and peritoneal dialysis, with selection guided by shared decision-making between patients and healthcare teams [4].

Muscle atrophy is a major complication of CKD, with both disuse and disease-related mechanisms contributing to reduced physical capacity, loss of functional independence, and increased risk of death [5]. Skeletal muscle plays a crucial role in movement, metabolism, respiration, and visceral protection [6]. Sarcopenia is particularly prevalent, with severe cases affecting 21% of people with CKD, rising to 26.2% in those on dialysis [7]. Loss of muscle strength, mass, and physical performance is even more widespread, with rates of 43.4%, 29.1%, and 38.6%, respectively [7]. The UK Renal Registry reported that 23% of individuals starting kidney replacement therapy (KRT) in 2021 were aged over 75 years [8]. Among people undergoing haemodialysis aged over 75, 18% were unable to walk, increasing to 77% in those classified as dependent [9].

Sarcopenia significantly elevates the risk of falling, with affected individuals up to 3.3 times more likely to experience falls [10]. This risk is compounded by the strong association between sarcopenia and osteopenia in older people with CKD, contributing to increased fracture rates [11, 12], and higher post-surgical death following knee, hip, and hemiarthroplasty procedures [13].

Beyond physical risks, CKD profoundly impacts quality of life (QoL). Up to 92% of non-dialysis CKD patients report limitations in daily activities, particularly walking (74%) and stair use (83%) [14]. People undergoing dialysis experience similar impairments [15]. Given its role in mobility decline and fall risk, sarcopenia is a key modifiable factor influencing QoL in CKD.

Description of the intervention and how it might work

Exercise therapy helps mitigate muscle deterioration in people undergoing dialysis [16], but traditional programmes are often limited by factors such as fatigue, time constraints, and low motivation [17]. Neuromuscular electrical stimulation (NMES) is an alternative that simulates both cardiovascular exercise [18] and strength training [19], commonly used in rehabilitation for conditions like stroke, cerebral palsy, and spinal cord injury [6, 20, 21, 22, 23]. It is thought to be an appropriate alternative or supplement to traditional means of exercise for the dialysis population [24].

Cyclic NMES, the focus here, induces muscle contractions without voluntary effort by using surface electrodes to stimulate motor neurones, generating neuromuscular overload similar to traditional exercise. Other NMES modes – sensory stimulation (below the motor threshold) and electromyography-triggered stimulation (initiating contractions when voluntary electromyographic signals exceed a threshold) – are less relevant for people undergoing dialysis. Regardless of modality, stimulation intensity must be 'maximal tolerable' to optimise benefits without excessive discomfort [23, 25].

A key advantage of NMES is its feasibility during dialysis, requiring minimal equipment compared to ergometers or resistance training [24]. People undergoing haemodialysis, who spend significant time sedentary during treatment (three sessions/week, four hours/session) [26], could benefit from NMES to counteract muscle atrophy.

NMES strengthens muscles by repeatedly activating motor neurones, triggering adaptations that increase muscle size and number. Mechanical stress from contractions stimulates protein synthesis, influenced by endocrine responses such as insulin-like growth factor 1 (IGF-1) release [27], while also modulating key pathways like the mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK), which regulate muscle protein turnover [28]. Additionally, NMES enhances neuromuscular co-ordination, improving voluntary movement efficiency in both healthy and clinical populations [29].

Why it is important to do this review

As muscle mass declines in individuals with CKD, the accompanying deterioration in overall health leads to increased healthcare costs and more complex care requirements [30]. Despite growing recognition of the issue, there remains a lack of clarity regarding the most effective interventions for mitigating muscle wastage and the specific mechanisms through which these interventions work. Current evidence is fragmented, with studies offering varying results and limited consensus on the best approaches to preserving muscle mass in people with CKD.

This review is particularly timely as the global burden of CKD continues to rise. In 2015, over 2.5 million people were receiving KRT, and this number is expected to more than double to 5.4 million by 2030, driven by increasing risk factors like hypertension and diabetes [31]. This anticipated increase in CKD prevalence is likely to result in a higher incidence of muscle wasting and associated complications, exacerbating the already significant strain on healthcare systems worldwide.

Given the rising global prevalence of CKD and the significant challenges it presents, there is a critical need to synthesise the existing evidence on interventions for muscle preservation in people with CKD. A systematic review will address the uncertainties in current findings, evaluate the effectiveness of different interventions, and provide a clearer understanding of the mechanisms involved. Additionally, considering the potential heterogeneity in intervention outcomes, subgroup analyses will be conducted based on the length of intervention protocols, stimulation settings and intensity. This will help to determine whether these variables influence the effectiveness of NMES in preserving muscle mass. By doing so, the review will help inform healthcare practices and contribute to more effective management strategies for this growing population.

OBJECTIVES

To assess the effects of neuromuscular electrical stimulation (NMES) on muscle structure and function in people undergoing dialysis.

METHODS

We will follow the Methodological Expectations for Cochrane Intervention Reviews when conducting the review [32], and use PRISMA 2020 for the reporting [33].

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) and cluster-RCTs investigating interventions using NMES on the lower limb. We will not exclude studies based on the year or language of publication.

Types of participants

We will include studies with participants over the age of 18 who have CKD, are pre-transplant, and are undergoing any form of dialysis. People undergoing either haemodialysis or peritoneal dialysis will be eligible. There will be no restrictions based on location, sex, dialysis type or duration. We will exclude participants receiving dialysis for any other reason; this includes acute kidney injury. Animal studies will not be eligible for inclusion.

If a study includes a subset of eligible participants, we will include it if we can determine from study data that the majority of the participants are eligible. If it is not possible to ascertain eligibility from published data, we will contact the original study authors.

Types of interventions

The types of studies we will include are those that use surface electrodes for intradialytic NMES of lower limb muscles. There will be no restrictions on the duration, intensity, or frequency of the stimulation per session or per protocol. However, we will exclude studies that only involve a single session of stimulation. The electrical stimulation can be implemented on people undergoing either haemodialysis or peritoneal dialysis in any setting, including inpatients or outpatients in a hospital, in the community or in a dialysis unit. In the case that a study utilises NMES in conjunction with another co-intervention that does not physically add or detract from the NMES intervention (e.g. creatine supplementation or a distraction technique), we will include it. If the co-intervention is physical (e.g. simultaneous cycling and NMES), we will exclude it.

Eligible studies will compare NMES with usual dialysis care or a placebo, though the stimulation can be given as one component of a rehabilitation programme as well as in isolation. We will include studies if they compare NMES to an exercise intervention, but only if there is also a control group. We will exclude the exercise group from the analysis.

Outcome measures

This review will prioritise patient-centred outcomes, aligning with the Standardised Outcomes in Nephrology (SONG) initiative [34]. In line with Cochrane Kidney and Transplant guidance, we will include these outcomes in the review regardless of whether data are reported in the included studies.

We will extract all outcomes reported in the included studies, and prioritise SONG-aligned outcomes during synthesis and interpretation.

Critical outcomes

The critical, patient-centred outcomes can be seen in Table 1; these focus on activity levels, muscle function and treatment experience.

Table 1. Critical outcome measures (aligned with SONG haemodialysis core outcomes)

SONG core domain	Example outcome measures
Life participation	Kidney Disease Quality of Life (KDQOL) Activity domain; return to daily activities
Fatigue	Patient-reported fatigue scales; post-treatment fatigue
Cardiovascular disease	Blood pressure; heart rate; arrhythmias (if reported)
Pain	Pain at stimulation site; general pain scores
Infection	Infection at electrode site (if reported)
Death	All-cause death (if reported)
Vascular access problems	Included if reported, although unlikely in NMES interventions

Important outcomes

The important outcomes (Table 2) that are of greater interest to clinicians and researchers aim to start understanding the changes that might be seen at the critical level and the potential side effects for participants.

Table 2. Additional important outcomes (commonly reported in NMES literature)

Outcome category	Example outcome measures
Muscle function	Leg extension strength; handgrip strength; one-rep max (1RM)
Functional performance	6-minute walk test; Sit-to-stand; Timed Up and Go
Muscle structure	Muscle cross-sectional area; thickness; pennation angle
Quality of life	SF-36 (36-item Short Form survey); KDQOL overall and domain-specific scores
Mechanisms (exploratory)	Creatine kinase; IL-6; IL-10; IGF-1; albumin
Treatment experience	Muscle soreness; skin irritation; patient satisfaction

Timing of outcome assessments

For studies reporting outcomes at multiple time points, we will only include baseline and postintervention measures to minimise selective reporting bias. We have selected these time points based on clinical relevance and importance for decision-makers.

Adverse events

We will extract data on the following adverse events: pain (including pain at the stimulation site), skin injury, muscle tear, hospitalisation, death, and participant withdrawal for any reason other than kidney transplantation. We will summarise adverse event data descriptively and consider it alongside the critical and important outcomes.

Search methods for identification of studies

Searches will not be restricted by date, language, or publication status.

Electronic searches

The Cochrane Kidney and Transplant Information Specialist will search the following databases for RCTs without language, publication year or publication status restrictions.

- Cochrane Kidney and Transplant Specialised Register via MeerKat (a software application built on Microsoft Access used to manage the database). MeerKat is a study-based register and is used to store bibliographic and study details, link multiple reports to a single study, link studies to reviews, and track the progress of reviews.
- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library
- Ovid MEDLINE ALL (from 1946)
- Embase.com records as part of the search of CENTRAL, as described in 'How CENTRAL is created' (www.cochranelibrary.com/central/central-creation)
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) as part of the search of CENTRAL
- World Health Organization International Clinical Trials Registry Platform (trialsearch.who.int) as part of the search of CENTRAL.

The Information Specialist will model the subject strategies for other databases on the search strategy designed for MEDLINE. MEDLINE searches combine the subject strategy adaptations with the sensitivity and precision maximising search strategy designed by Cochrane for identifying RCTs (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [35]) and updated by us to account for new MeSH study types and wider use of machine indexing by the National Library of Medicine (NLM). We present the MEDLINE, Embase and CENTRAL subject search strategies in Supplementary material 1.

Searching other resources

- We will check the reference lists of included studies and any relevant systematic reviews identified for further references to relevant studies.
- We will check the included studies for retractions and errata via the Retraction Watch Database and report the search dates in the review (retractiondatabase.org).
- We will search Epistemonikos for related systematic reviews (www.epistemonikos.org).
- We may contact the original authors or funders of included studies for clarification and further data if study reports are unclear.

Data collection and analysis

Selection of studies

All identified titles and abstracts of records obtained will have duplicates automatically removed using reference management software [36]. Two individuals will then screen these independently to remove obviously irrelevant papers. We will obtain full texts for the remaining papers, and two individuals will screen them, again independently, using the review inclusion and exclusion criteria. Where a full text is unavailable, we will contact authors for the source publication. Any disagreements during any stage of this process will be resolved through discussion with a third author. We will follow PRISMA guidelines, recording and documenting details of each stage of the process.

Data extraction and management

At least two authors will work independently to extract data from included studies, using a pre-prepared data collection form. Disagreements will be resolved through discussion with

a third author. Authors will pilot the data collection form prior to use. We will collect data on study design, comparators, participant characteristics, electrode placement, stimulation settings, intervention length, outcome measures, results, and adverse events. Authors will collect these data independently to avoid bias. Where data are unavailable, we will contact authors.

We will extract the sample size, mean, and standard deviation, where reported, to quantify effect size as a standardised mean difference. In the cases where means are reported with 95% confidence intervals or standard error of the mean, we will estimate the standard deviation from these data. If the median and interquartile range (IQR) are reported, we will contact study authors to obtain raw data. If this is not possible, we will assume the median to be the mean and calculate the standard deviation as the IQR divided by 1.35 [37].

Risk of bias assessment in included studies

We will use the Cochrane RoB 2 Excel tool to assess bias in the included studies, for the intention-to-treat effect [38]. We will give specific attention to bias arising from the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result [39].

Two authors will assess the studies for risk of bias, answering signalling questions independently. They will make a judgement for each of the domains, and subsequently make an overall risk of bias judgement. Judgements will fall under low risk of bias, some concerns, or high risk of bias. Any disagreements will be resolved through discussion with a third author. The lead author will contact study authors to obtain or clarify information.

Measures of treatment effect

Using data from included studies, we will measure the treatment effect using the mean difference (MD) when outcomes are reported on the same scale and are directly comparable, or the standardised mean difference (SMD) when outcomes are measured on different scales or using different instruments, depending on the available data [37]. The comparisons to be made will be between the control and experimental groups for pre- and post-conditions in the case of a randomised control trial. We will report outcomes with 95% confidence intervals (CI).

We will summarise the comparisons using forest plots, which will aid the understanding of the impact of the intervention on the different outcome measures. Even so, we will consider the treatment effect alongside other study parameters, including baseline similarities, characteristics of the intervention per study, adverse reactions, and sample size.

Unit of analysis issues

In the case of RCTs with three or more arms (expected to be NMES, exercise and control groups), we will exclude the exercise group or the third arm from consideration in the review. Following guidance from the *Cochrane Handbook for Systematic Reviews of Interventions,* we will analyse any cluster-RCTs at the cluster level to avoid unit-of-analysis issues [40].

Dealing with missing data

In cases of missing data, we will contact the authors of the original study. At this stage, we anticipate that missing values will account for less than 20% in each study. If missing data exceed this threshold, a decision on whether to exclude the study will be made on a case-by-case basis, guided by the RoB 2 criteria.

Where raw data are available, we may employ imputation methods to address singular missing values. For missing values between two data points, we will use the mean of the adjacent values [41]. Alternatively, if only an initial value is available, we may apply the last value carried forward method. If data imputation is necessary, we will conduct sensitivity analyses to evaluate the impact of imputed data on the results.

Reporting bias assessment

The search strategy will be appropriately broad to ensure the identification of all relevant studies, both published and unpublished. We will assess all included studies for risk of bias, in addition to data reporting bias, by comparing them to registered trials or published protocols where available. Where 10 or more studies are available for an analysis, we will use funnel plots to assess the potential for reporting bias. Two independent authors will assess the risk of bias due to missing results using the ROB 2 tool for RCTs, with disagreements resolved by a third. We will contact authors to confirm reported results where there are uncertainties. If no response is given, we will exclude the results of that study.

Synthesis methods

A meta-analysis will be conducted to establish which outcome measures may be influenced by NMES. Where data are available for the same outcome measure in multiple studies, we will pool the data and conduct a meta-analysis. We will compare the control group with the NMES intervention groups. Depending on outcome measures, we will use either MD or SMD to conduct the meta-analysis. For all analyses, we will use Review Manager and present results using forest plots [42]. As this review aims to investigate what outcomes have been investigated previously, at this point, it is unclear which outcomes will have sufficient data to conduct a meta-analysis.

We anticipate that we will use a random-effects model for analysis due to the inherent heterogeneity between studies for variables that will not be controlled for, including but not limited to time on dialysis, dialysis efficiency, epidemiology of CKD, age, prior exercise experience, and activity levels outside of dialysis. Where meta-analysis is not possible, such as due to significant differences in study designs, inadequate or inconsistent data, small numbers of studies, or incompatible outcome measures, we will conduct a structured qualitative synthesis. This will follow the Synthesis Without Meta-analysis (SWiM) reporting guidance [43, 44], to ensure a transparent and reproducible approach to summarising effect estimates across studies.

Investigation of heterogeneity and subgroup analysis

Preliminary searching suggests that a subgroup analysis will not be possible. However, if it is possible, then we will conduct an analysis using RevMan's formal tests for subgroup differences to investigate whether effect size varies with:

- length of intervention protocol;

- stimulation settings and intensity.

Methodological variation within treatment methods, experimental design or responses to treatment can result in heterogeneity. As such, we will use data collection forms to extract data relating to the methods used, and present these in a tabular format. Preliminary searching suggests high levels of heterogeneity to be present both clinically and statistically. Therefore, we will report treatment response variations using the I^2 statistic with a score of less than 40% deemed to be insignificant heterogeneity [45]. We will conduct a sensitivity analysis for studies with a high I^2 to explore potential sources of variability. We will do this by excluding studies with differing methodologies, populations, or intervention characteristics to assess their impact on the overall results.

Equity-related assessment

We will not investigate health inequities in this review, as it focuses on the effects of the intervention rather than its implementation. Additionally, the review does not specifically address disadvantaged populations, a particular health condition, or outcomes where equity considerations would be relevant to the research question.

Sensitivity analysis

We will conduct a sensitivity analysis by excluding studies assessed as having an overall high risk of bias using the criteria specified in the RoB 2 tool, to evaluate the effect of their exclusion on the calculated effect size. We will classify studies as having an overall high risk of bias if they are rated as high risk in at least one domain or if concerns across multiple domains collectively lead to an overall judgment of high risk, as defined by the RoB 2 framework.

Certainty of the evidence assessment

Two review authors will independently assess the certainty of evidence for the critical outcomes listed in Table 1 using the GRADE approach [46]. This assessment will evaluate risk of bias, consistency of effect, imprecision, indirectness, and publication bias, following the criteria outlined in the GRADE Handbook [46]. The overall risk of bias judgements, determined using the RoB 2 tool, will be incorporated into the GRADE assessment. Using GRADEpro software, we will classify the certainty of evidence for each outcome as high, moderate, low, or very low [47].

We will present a summary of findings table in accordance with section 14.1.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* [48], reporting only the critical outcomes aligned with the SONG core outcome domains: life participation, fatigue, cardiovascular disease, pain, infection, mortality, and vascular access problems.

Consumer involvement

People with CKD will not be directly involved in this review due to limited resources. However, the selected outcomes align with the SONG core outcomes [34], which were developed with consumer involvement and are further supported by previous patient and public involvement work highlighting the importance of muscle function to patients.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016155.

Supplementary material 1 Search strategies

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

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The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Giovanni FM Strippoli, Department of Precision and Regenerative Medicine and Jonian area (DIMEPRE-J) University of Bari, Italy; School of Public Health, University of Sydney, Australia
- Managing Editor (selected peer-reviewers, provided editorial guidance to authors, edited the article): Sara Hales-Brittain, Central Editorial Service; Pricivel Carrera, Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Jacob Hester, Central Editorial Service
- Copy Editor (copy editing and production): Andrea Takeda, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): João Luiz Quaglioti Durigan, University of Brasília, Brazil (clinical/content review); Brian Duncan (consumer review); Jo-Ana Chase, Cochrane Evidence Production and Methods Directorate (methods review); Sarah Louise Klingenberg, Cochrane Hepato-Biliary Group (search review). One additional peer-reviewer provided clinical/content peer-review but chose not to be publicly acknowledged.

Contributions of authors

LB: Protocol design, write-up.
SD, AP: Protocol design, reviewing manuscript.
AH: Clinical input, reviewing manuscript.

Declarations of interest

LB: Employment at Bournemouth University and no commercial or non-commercial conflicts of interest relevant to this review.

SD: Employment at Bournemouth University and no commercial or non-commercial conflicts of interest relevant to this review.

AH: Fiduciary Officer at Dialysis UK CIC and Chief Medical Officer at Dorset County Hospital Foundation Trust.

AP: Employment at Bournemouth University and co-author of a study that is likely to be included in the review.

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External sources

- None, Other

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Registration and protocol

Cochrane approved the proposal for this review in March 2024.

Data, code and other materials

Data sharing not applicable to this article as it is a protocol, so no datasets were generated or analysed.

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