PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Aerobic Neuron-Muscular Electrical Stimulation – an emerging technology to improve haemoglobin A1c in type 2 diabetes mellitus; results of a pilot study
AUTHORS	L.Crowe and B.Caulfield

VERSION 1 - REVIEW

REVIEWER	Carmen Castaneda-Sceppa, MD, PhD Associate Professor of Health Sciences Bouve College of Health Sciences Northeastern University 360 Huntington Avenue Boston, MA 02115 United States of America
REVIEW RETURNED	18/10/2011

THE STUDY	The study led by these investigators uses innovative technology via a neuromuscular electrical stimulation (NMES) device as the basis for aerobic training in a group of men with type 2 diabetes. The study is a pilot investigation with a small group of 8 subjects enrolled in the intervention without use of a comparison group. As I understand it, even though this technology is not new, it is novel and its feasibility and acceptability by people with diabetes may not be established. The investigators were interested in determine the efficacy of aerobic NMES. However, this is not possible given the study design. The study outcome was Haemoglobin A1c levels pre and post study over a period of 6 weeks. The authors observed a significant improvement in A1c levels. However, given the study design it is not possible to conclude with certainty on the level of evidence derived from this pilot study. Additionally, there are substantial revisions to be made to clarify methodology, statistical analysis, data collection and study limitations. Therefore, I recommend for this paper to be considered for publication in BMJ Open as a brief report, provided the suggested revisions are satisfactorily addressed.
RESULTS & CONCLUSIONS	This is a pilot study without a RCT that can not provide conclusive efficacy data.
GENERAL COMMENTS	The objective of this pilot investigation was to see if it could be used by a sample of diabetic men and assess the efficacy of this new technology on Haemoglobin A1c levels. Eight diabetic men trained 6 times weekly for 6-8 weeks using NMES parameters, unsupervised, at home. Haemoglobin A1c, body mass and composition were measured before and after the NMES intervention period. There were no other medication or lifestyle changes and a short questionnaire was filled in at the end. The authors found that A1c levels improved by 0.8 ± 0.7% (p=0.01). Weight loss was 0.7 ± 2.7kg and lean mass gain was 808 ± 1762g. All participants considered the system suitable for diabetics, would recommend it and would continue to use it twice a week “to maintain improvements”. The

	investigators concluded that results suggest that aerobic NMES may have a beneficial effect on A1c of men with diabetes. The treatment may be of particular benefit in those who will not or cannot do adequate amounts of voluntary exercise. After careful review of the study, some important revisions are suggested as follows. 1) The abstract refers to weight loss and lean mass gains. However, there were no statistically significant differences in the pre-post values by paired- t-test. Please add p values for clarity regarding the inference of the estimations. 2) The authors refer to this as the “first study to used these new NMES techniques” (page 4. Line 52). However, given this is a pilot investigation not based on a randomized controlled trial (RCT) the enthusiastic characterization of this statement should be reconsidered. 3) There needs to be a description of how many subjects were approached for those ultimately enrolled in the study. How many refusals, drop outs, etc. Given the small sample size this information is needed to make sure that subjects who chose to enroll in the study were not different from those who refused in terms of their motivation, self management and health consciousness…because all of which would bias the results toward a benefit. 4) Regarding the aerobic NMES intervention: How was accommodation and habituation to the NEMS device tested? How was breathing and sweat quanti/qualified by the subjects? How was the target heart rate of 120 determined? How long was the introductory session? Where there any drop puts after it? 5) The main outcome, A1c, is based on an n of 8 where one subject’s data was calculated from fructosamine. I suggest the analysis is only based on the 7 subjects for whom A1c data are available pre and post study. 6) How was the qualitative data of the questionnaire handled? Were measured taken in a blinded fashion? 7) There needs to be a section on statistical analysis in the methods. 8) The last sentence of the first paragraph in the discussion alludes to the lack of change in diet or lifestyle. However, there were not data collected on dietary intake or physical activity to back this up. 9) Given the sample size and study design, this pilot study can not conclusively provide evidence base information on the efficacy of aerobic NMES. Therefore, I suggest the discussion be revised to take into account these study limitations, which should also be mentioned. 10) Add p values to Table 1 and a foot note on statistical analysis.

REVIEWER	Dr Rob Andrews Consultant Senior Lecturer in Diabetes and Endocrinology University of Bristol

	Early ACTID office Joint Clinical Research Unit Level 5, Old Building, Near Ward 29 Bristol Royal Infirmary Marlborough Street Bristol BS2 8HW United Kingdom I lead a research group that develops and tests diet and exercise programmes to help in the prevention and treatment of Diabetes.
REVIEW RETURNED	04/07/2011

THE STUDY	I am unclear as to how the participants for this study were selected and how representative they are of the average patients with diabetes. More detail in needed about the selection process and about the demographics of the patients, for example • Why were only men examined? • Why were the particular inclusion criteria chosen? • How were “suitable potential patients chosen”? • How many people volunteered and what were the reasons for not being included? • What medication were the patients on? Why was 6-8 weeks used, as HbA1c normally takes longer than that to improve? I am unclear as to whether they were asked to use it for 6 or 8 weeks. Figure 1 is difficult to follow Statistics – there is no mention of power, In other words with 8 patients what difference in HbA1c are you powered to see?
RESULTS & CONCLUSIONS	Results Normally I would expect to see some demographic description of the patients who were entered into the study. Is it possible to see this information? I think it is essential to have details of the adherence to the program. For example what percentage of patients used the NMES 6 times a week? What was the mean length of usage of the NMES and if less than the set time why? One patient does much better than the others with a fall of HbA1c by 2% if this patient is removed from the analysis does this effect the result? Discussion There needs to be more discussion about their results and how these compare to other studies. The effect is very varied some patients seeing a 2% fall others seeing no effect. Similarly some patients are gaining huge amount of lean mass and others losing lean mass. Why such differences? In this study patients had to use the machine 6 times a week, where as in exercise studies they are typically asked to exercise 3 times a week. Is there any data on long term adherence to these machines and this frequency of use?

	What are the next steps to validate the use of these machines?
GENERAL COMMENTS	I thought this paper by Crowe et al was thought provoking and very interesting. This paper found that a new neuromuscular electrical stimulation (NMES) device improved HbA1c in 8 patients with diabetes. My comments would be as follows; General I would suggest that the Authors refer to the participants as “patients with diabetes” and not as “diabetics”. Abstract Read well but could we clarify how long the intervention was for – was it 6 or 8 weeks? Seems unlikely that this was not standardised. Introduction It would be nice to have more detail on how this new device differs from those previously used, what the cost of this system is and what are the known side-effects. Could a picture of the device be provided or a website link to readers can get an idea of what the device looks like? I am not sure that arthritis has been shown to be an impediment to exercise, data does suggest that it may reduce uptake of exercise regimes but not that it prevents it completely. Descriptions of measures should be consistent – HbA1c or glycosylated haemoglobin. Could the following wording be looked at; • Impediment – this is a term usually used for speech • “Aggressive intensities” – do you mean this • “in the obese” – should it not be in the patient with obesity. • “…using their system” – this reads like they are your competitors – should it not be “..using other systems”. Patients and Methods I am unclear as to how the participants for this study were selected and how representative they are of the average patients with diabetes. More detail in needed about the selection process and about the demographics of the patients, for example • Why were only men examined? • Why were the particular inclusion criteria chosen? • How were “suitable potential patients chosen”? • How many people volunteered and what were the reasons for not being included? • What medication were the patients on? Why was 6-8 weeks used, as HbA1c normally takes longer than that to improve? I am unclear as to whether they were asked to use it for 6 or 8 weeks. Were any measures of activity or diet measured during the study? Figure 1 is difficult to follow Statistics – there is no mention of power, In other words with 8 patients what difference in HbA1c are you powered to see?

	Results Normally I would expect to see some demographic description of the patients who were entered into the study. Is it possible to see this information? I think it is essential to have details of the adherence to the program. For example what percentage of patients used the NMES 6 times a week? What was the mean length of usage of the NMES and if less than the set time why? One patient does much better than the others with a fall of HbA1c by 2% if this patient is removed from the analysis does this effect the result? Discussion There needs to be more discussion about their results and how these compare to other studies. The effect is very varied some patients seeing a 2% fall others seeing no effect. Similarly some patients are gaining huge amount of lean mass and others losing lean mass. Why such differences? In this study patients had to use the machine 6 times a week, where as in exercise studies they are typically asked to exercise 3 times a week. Is there any data on long term adherence to these machines and this frequency of use? What are the next steps to validate the use of these machines?

REVIEWER	Makii (Mark) Muthalib, PhD Post-doctoral Fellow Institute of Health & Biomedical Innovation Queensland University of Technology Australia
REVIEW RETURNED	17/10/2011

GENERAL COMMENTS	Title: “NMES” should be spelled out Abstract P.2.L.27-29: Specify the approximate duration of the NMES session and NMES parameters utilised (stimulation parameters [on-off cycle, amplitude and frequency] and muscles stimulated). P.2.L.33: Specify the details of the questionnaire Introduction P.3.L.6-9: provide references for the first sentence. P.3.L.44: NMES abbreviation already described. P.3.L.46-51: Indicate any other “sophisticated NMES systems” and a new sentence should be added here to describe the main differences of the “sophisticated NMES” to “traditional NMES” systems (such as stimulation parameters [muscles, amplitude, frequency, on-off cycle]). P.4.L.3-10: Specify what “aggressive intensities” and “low level NMES” refer to. P.4.L.16: First use of abbreviation “HbA1C” should be spelled out. Also, a new sentence should be added to indicate the importance of measuring HbA1C levels in diabetic patients.

	P.4.L.36-39: Describe what “aerobic exercise NMES systems” refers to and what is the “recommended exercise dose”? P.4.L.51: Describe the “pulse patters” used? Methods The Methods section should be split into different sub-headings, such as “participants” and “procedure”, also details of the “Statistical Analysis” needs to be described. P.5.L.13-21: It would be better to indicate the number of participants here and also specify the age, height, weight and BMI as Mean (SD) instead of range. The activity level of each participant should also be described, since this could be a confound to the actual benefit of the NMES intervention over the 6-8 weeks. P.5.L.19: Specify the details of typical “oral medications”? P.5.L.34-36: What were the stimulation parameters used to reach the ~120BPM heart rate in the introductory session, and were these stimulation parameters used by each subject for their individual NMES training sessions? P.5.L.45-49: Provide details of how HbA1C was measured and what were the exact time points of pre- and post- data collection. P.6.L.15-18: Specify the manufacturer details of the NMES system, electrode size and locations on the thigh muscles. P.6.L.31: Specify how many of each frequency pattern (5 or 19Hz) was utilised by the subjects? Results P.6.L.43: specify the table number Discussion P.8.L.29-39: Did any of the participants exercise during the course of the NMES intervention? P.9.L.3-21: Further description of the specific muscle activation profile and metabolism of NMES compared to voluntary exercise should be provided in this section. The recent paper by Gondin et al. (J Apply Physiol, 110:433-450, 2011) provide details of the fibre type and metabolic adaptations to NMES training.

VERSION 1 – AUTHOR RESPONSE

VERSION 2 – REVIEW

REVIEWER	Carmen Castaneda Sceppa, MD, PhD Associate Professor and Director, Graduate Program in Exercise Science Bouve College of Health Sciences Northeastern University Boston, MA USA
REVIEW RETURNED	23/12/2011

THE STUDY	I have reviewed the revised manuscript. However, this was hard to do given that I do not have a point-by-point response of the changes made to the manuscript per reviewer’s recommendations. Additionally, I suggested the manuscript should be revised to reflect a brief report. However, the revised manuscript seems larger than

	the original one. However, more importantly, I am not comfortable with the description of results and benefits of NMES presented given that these findings are based on a very small sample (n=6 completed subjects) in a study that only has the participants undergoing NMES without a control group. I have not provided specific comments to the authors because I can't follow the changes made to determined whether they seem satisfactorily addressed.
RESULTS & CONCLUSIONS	As indicated above the findings from this pilot small study are questionable.

REVIEWER	Dr Robert Andrews Consultant Senior Lecturer in Diabetes and Endocrinology University of Bristol Early ACTID office Joint Clinical Research Unit Level 5, Old Building, Near Ward 29 Bristol Royal Infirmary Marlborough Street Bristol BS2 8HW I am the lead of a research group that develops and tests diet and exercise programmes to help in the prevention and treatment of diabetes.
REVIEW RETURNED	29/12/2011

THE STUDY	Patients in this study not entirely representative of the general population of patients with Diabetes. But this is a proof of concept study so not essential to do so.
GENERAL COMMENTS	The authors have addressed all of the questions and issues that I brought up at my last review. I though that this reads very well and clearly describes what was done.

VERSION 2 – AUTHOR RESPONSE