PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Muscle stimulation in advanced idiopathic pulmonary fibrosis: a randomised placebo-controlled feasibility study
AUTHORS	Nolan, Claire; Patel, Suhani; Barker, Ruth; Walsh, Jessica; Polgar, Oliver; Maddocks, Matthew; George, Peter M; Renzoni, Elisabetta A.; Wells, Athol; Molyneaux, Philip; Kouranos, Vasilis; Chua, Felix; Maher, Toby; Man, William

VERSION 1 – REVIEW

REVIEWER	Cohen, Judith Hull York Medical School, Hull Health Trials Unit
REVIEW RETURNED	01-Mar-2021

GENERAL COMMENTS	This is an important study reporting the results of a feasibility study of neuromuscular electrical stimulation (NMES) in advanced IPF. Although NMES is included in NICE guidance as a possible alternative treatment for IPF patients who are unable to participate in pulmonary rehabilitation, there is limited evidence of use in this population. This study highlights some issues with the feasibility of conducting a larger RCT including recruitment and the use of a sham device as a placebo, which will help inform future RCT design. The study design, outcomes and reporting are appropriate for a feasibility study. The primary outcomes are feasibility outcomes and are reporting using descriptive statistics with no formal statistical between-group testing. Summary results are tabulated with a narrative description of within and between group trends observed. Recruitment to the qualitative component was limited and resulted in inclusion of only one participant from the control group but this is clearly described as a limitation to the study. The manuscript follows the CONSORT extension for pilot and feasibility studies, and the checklist has been completed. I recommend that this manuscript is accepted for publication, with some recommendations for minor revision as outlined below. Introduction: 1) There is a recent trial registered with ISRCTN which would be useful to acknowledge within the introduction: NCT03830250. This is currently underway and so will not have an impact on the results reported in this manuscript. Methods: 2) Title study design and subjects – would recommend change from subjects to participants 3) The intervention is a device, recommend that the authors state whether this is being used in accordance with current CE-Mark, as otherwise unclear whether the study should have been notified to the MHRA.

	4) The main elements of the home exercise manual are briefly described in the appendix, but this is not a full manual that would easily enable replication. Would it be possible to state whether the exercise manual could be provided on application to the authors, or is available in full elsewhere? Results: 5) Fig.1 CONSORT diagram, there are some errors in the list of patients excluded, the sum of the individual reasons for exclusion do not match the total figure. Please check and correct.

REVIEWER	Nojima, Masanori the Institute of Medical Science, the University of Tokyo, Center for Translational Research
REVIEW RETURNED	11-Mar-2021

GENERAL COMMENTS	There are no major problems with the design or implementation of this clinical trial. However, it should be clearly stated in the abstract and the conclusion which outcome results are critical for the interpretation of "not feasible". It is simply said the no feasibility of “this protocol," but it is hard to understand what exactly was wrong with it (at least it cannot be derived from the abstract). Based basic understanding, the problem was poor adherence in the placebo group? If so, why was there poor adherence, what factors contributed to it, and what are the authors planning to do to improve it for the further study?

REVIEWER	Kamiya, Hiroyuki Tatebayashi Kosei Hospital, Department of Respiratory Medicine
REVIEW RETURNED	14-Mar-2021

GENERAL COMMENTS	Thank you for inviting me to review the manuscript entitled “Muscle stimulation in advanced idiopathic pulmonary fibrosis: a randomised placebo-controlled feasibility study”. This is a pilot trial accompanied by a subsequent qualitative analysis to see if a formal future trial is feasible. As there is a limitation of benefits obtained by pharmacological therapy for patients with IPF, it is important to consider the potential of other types of interventions. The authors focused on NMES as a promising candidate. Overall, the study was well designed and conducted. I would request only minor clarifications. 1. Inclusion criteria Quadriceps maximum voluntary contraction (QMVC)<80% predicted What is the reference value of QMVC (%predicted)? or where is it available? 2. Table 2 Please add DLCO (% predicted). Please add QMVC (% predicted). Please add the number of participants who used corticosteroids if any. 3. Qualitative analysis Although a sample size of ten was chosen a priori, only six participants including only one from a placebo group were invited to the qualitative interviews. This is a major limitation. Could you please explain why this event occurred and discuss in more details the impact of this limitation? 4. Other points

	Could you please mention anywhere in the manuscript the relationship between pulmonary function parameters and QMVC or rectus femoris cross-sectional area?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 comments:

C1: "This is an important study reporting the results of a feasibility study of neuromuscular electrical stimulation (NMES) in advanced IPF. Although NMES is included in NICE guidance as a possible alternative treatment for IPF patients who are unable to participate in pulmonary rehabilitation, there is limited evidence of use in this population. This study highlights some issues with the feasibility of conducting a larger RCT including recruitment and the use of a sham device as a placebo, which will help inform future RCT design. The study design, outcomes and reporting are appropriate for a feasibility study. The primary outcomes are feasibility outcomes and are reporting using descriptive statistics with no formal statistical between-group testing. Summary results are tabulated with a narrative description of within and between group trends observed. Recruitment to the qualitative component was limited and resulted in inclusion of only one participant from the control group but this is clearly described as a limitation to the study. The manuscript follows the CONSORT extension for pilot and feasibility studies, and the checklist has been completed. I recommend that this manuscript is accepted for publication, with some recommendations for minor revision as outlined below."

R1: Thank you for this feedback.

C2: "Introduction: There is a recent trial registered with ISRCTN which would be useful to acknowledge within the introduction: NCT03830250. This is currently underway and so will not have an impact on the results reported in this manuscript."

R2: Thank you for this feedback. We were unable to find the study reference on ISRCTN or clinicaltrials.gov. However, we did find a study currently recruiting people with IPF to a randomised controlled trial comparing NMES plus aerobic exercise to sham NMES plus aerobic exercise on clinicaltrials.gov, reference NCT03890250. We have amended the introduction to include this study.

C3: "Methods: Title study design and subjects – would recommend change from subjects to participants."

R3: Thank you, we have amended the manuscript.

C4: "Methods: The intervention is a device, recommend that the authors state whether this is being used in accordance with current CE-Mark, as otherwise unclear whether the study should have been notified to the MHRA."

R4: Thank you. Both the placebo and active NMES devices used in this study were used in accordance with their CE-mark, therefore, we were not required to notify the MHRA.

C5: "Methods: The main elements of the home exercise manual are briefly described in the appendix, but this is not a full manual that would easily enable replication. Would it be possible to state whether the exercise manual could be provided on application to the authors, or is available in full elsewhere?

R5: Thank you for this feedback. We have amended the online supplement to state that the home exercise manual can be provided on application to the authors.

C6: "Results: Fig.1 CONSORT diagram, there are some errors in the list of patients excluded, the sum of the individual reasons for exclusion do not match the total figure. Please check and correct.

R6: Thank you for spotting this, we have amended Figure 1.

Reviewer 2 comments

C7: "There are no major problems with the design or implementation of this clinical trial. However, it should be clearly stated in the abstract and the conclusion which outcome results are critical for the interpretation of "not feasible". It is simply said the no feasibility of "this protocol," but it is hard to understand what exactly was wrong with it (at least it cannot be derived from the abstract). Based on basic understanding, the problem was poor adherence in the placebo group? If so, why was there poor adherence, what factors contributed to it, and what are the authors planning to do to improve it for the further study?"

R7: Thank you for this feedback. As outlined in the discussion section, we considered the multiple reasons that a definitive trial using this protocol is not feasible. These include challenges in participant recruitment as well as between-group differences in retention of, treatment adherence and blinding of participants in the control compared to the intervention group. Owing to word count limitations, we have amended the abstract to only include the principle reason the protocol is not feasible for effectiveness testing: challenges in participant recruitment.

In the discussion section, we also suggest numerous proposals for alterations to the methodology that may help future studies to overcome the challenges we experienced

Reviewer 2 comments

C8: "Thank you for inviting me to review the manuscript entitled "Muscle stimulation in advanced idiopathic pulmonary fibrosis: a randomised placebo-controlled feasibility study". This is a pilot trial accompanied by a subsequent qualitative analysis to see if a formal future trial is feasible. As there is a limitation of benefits obtained by pharmacological therapy for patients with IPF, it is important to consider the potential of other types of interventions. The authors focused on NMES as a promising candidate. Overall, the study was well designed and conducted. I would request only minor clarifications."

R8: Thank you for this feedback.

C9: "Inclusion criteria: Quadriceps maximum voluntary contraction (QMVC)<80% predicted What is the reference value of QMVC (%predicted)? or where is it available?"

R9: Thank you for this feedback. We have added the reference to the manuscript.

C10: "Table 2: Please add DLCO (% predicted); Please add QMVC (% predicted); Please add the number of participants who used corticosteroids if any"

R10: Thank you for these suggestions. We have added data on DLCO, QMVC %predicted and the number of participants prescribed a corticosteroid to Table 2.

C11: "Qualitative analysis: Although a sample size of ten was chosen a priori, only six participants including only one from a placebo group were invited to the qualitative interviews. This is a major limitation. Could you please explain why this event occurred and discuss in more details the impact of this limitation?"

R11: Thank you for this feedback. We have amended the discussion section of the manuscript to explain why only one participant allocated to the control group took part in the qualitative interviews and the additional impact it has on the feasibility of the study as well as the interpretation of the results.

C12: "Other points: Could you please mention anywhere in the manuscript the relationship between pulmonary function parameters and QMVC or rectus femoris cross-sectional area?"

R12: Thank you for this feedback. Whilst the question you raise is very interesting, investigating the relationships between the parameters you describe was not an objective of this feasibility study, therefore we do not consider it appropriate to include these data in the manuscript. Instead we have outlined these data in the table below. The data do support our design choice to restrict recruitment to those with evidence of limiting breathlessness and muscle weakness.

Table 1. Relationship between lung function parameters and QMVC and RFCSA

	QMVC (kg)	*Rectus femoris cross-sectional area (mm^2)*
FVC (L)	*0.75 (<0.01)*	*0.82 (<0.01)*
FVC (% predicted)	*0.46 (0.15)*	*0.75 (<0.01)*
DLCO (ml/min/mmHg)	*0.30 (0.24)*	*0.38 (0.14)*
DLCO (% predicted)	*0.09 (0.73)*	*0.24 (0.36)*

Data analysed using Spearman's rank test.

Data reported as r-value (p-value).

Abbreviations: DLCO: Diffusing Capacity of the Lung for Carbon Monoxide; FVC: Forced Vital Capacity, QMVC: Quadriceps Maximum Voluntary Contraction; RFCSA: Rectus Femoris Cross-Sectional Area.

Thank you very much for considering the revised manuscript for publication in BMJ Open. We hope that we have answered all the reviewers' comments satisfactorily and would be very happy to provide any further clarification, comments or changes as necessary. Owing to the requests made by the reviewers the word count has increased to 4104 words.

VERSION 2 – REVIEW

REVIEWER	Cohen, Judith Hull York Medical School, Hull Health Trials Unit
REVIEW RETURNED	14-May-2021

GENERAL COMMENTS	I previously reviewed this manuscript and I thank the authors for responding to the reviewer comments. I am satisfied that the authors have responded in full and now recommend this paper for publication. This is an important study reporting the results of a feasibility study of neuromuscular electrical stimulation (NMES) in advanced IPF. Although NMES is included in NICE guidance as a possible alternative treatment for IPF patients who are unable to participate in pulmonary rehabilitation, there is limited evidence of use in this population. This study highlights some issues with the feasibility of conducting a larger RCT including recruitment and the use of a sham device as a placebo, which will help inform future RCT design. The study design, outcomes and reporting are appropriate for a feasibility study. The primary outcomes are feasibility outcomes and are reporting using descriptive statistics with no formal statistical between-group testing. Summary results are tabulated with a narrative description of within and between group trends observed. Recruitment to the qualitative component was limited and resulted in inclusion of only one participant from the control group but this is clearly described as a limitation to the study. The manuscript follows the CONSORT extension for pilot and feasibility studies, and the checklist has been completed.

REVIEWER	Nojima, Masanori the Institute of Medical Science, the University of Tokyo, Center for Translational Research
REVIEW RETURNED	13-May-2021

GENERAL COMMENTS	The phrase "Primarily owing to recruitment difficulties," inserted in the abstract makes it easier to understand the interpretation of the study results. There are no further problems that need to be addressed.

REVIEWER	Kamiya, Hiroyuki Tatebayashi Kosei Hospital, Department of Respiratory Medicine
REVIEW RETURNED	16-May-2021

GENERAL COMMENTS	The authors addressed all the questions raised earlier. I am satisfied with their response.