Dear Medical Research Council,

When were the MRC informed, in accordance with their guidelines, that the PACE Trial (PD White et al) Primary Outcome Measures of 'Positive Outcome' and 'Recovery' were to be eliminated from the Research Protocol?

Please provide any of the following which you have available:

1/ the date.
2/ a copy of the communication.
3/ the explanation/justification for the changes.
4/ the date and correspondence when the MRC approved the changes.

Yours faithfully,

Peter Kemp

MA
Dear Mr Kemp,

MRC Reference: FOIA 2016-035

Thank you for your request for information relating to the Primary Outcome Measures of the PACE Trial.

The Medical Research Council (MRC) outlines its expectations for the management of clinical trials in the published MRC Guidelines for Good Clinical Practice in Clinical Trials ([1](http://www.mrc.ac.uk/documents/pdf/good-...)).

Paragraph 5.2.1 (Compliance with protocol, page 17) states:

The trial should be conducted in accordance with the proposal funded by the MRC (and the protocol approved by the TSC) and favourably reviewed by the relevant ethics committees. It is the ultimate responsibility of the Principal Investigator to ensure that this happens. Any material amendments or alterations to or deviations from the protocol which affect the scientific or ethical basis of the trial, which could affect the personal integrity and/or welfare of trial participants, or which could have resource implications must have approval of the relevant ethics committee and the Trial Steering Committee (or the agreed alternative source of independent advice) before their implementation. The MRC should be notified of all material changes.

The primary outcomes that were outlined in the application that was considered by the Health Services and Public Health Research Board which allocated the MRC’s funding to the PACE Trial were:

- Fatigue (as measured by the Chalder Fatigue Questionnaire), and
- Physical function (as measured by the SF-36 physical function sub scale).

The terms “positive outcome” and “recovery” are not used.

The primary outcomes in the published protocol ([2](http://bmcneurol.biomedcentral.com/artic...)) were the same as those in the application (fatigue and physical function). The term “positive outcome” is mentioned in connection to these primary outcomes:

- “A positive outcome will be a 50% reduction in fatigue score, or a score of 3 or less, this threshold having been previously shown to indicate normal fatigue.”
- “We will count a score of 75 (out of a maximum of 100) or more, or a 50% increase from baseline in SF-36 sub-scale score as a positive
outcome.

The term “recovery” is mentioned as a secondary outcome.

In the Lancet paper ([3](http://www.thelancet.com/journals/lancet...)), which published the main results of the trial, the terms fatigue and physical function were not used. However the primary outcomes were reported in relation to the scales in the original application (Chalder Fatigue Questionnaire and SF-36). There was one change between the published protocol and the publication of results in that the analysis of the Chalder Fatigue Questionnaire was undertaken on a 0,1,2,3 scale instead of 0,0,1,1. The use of the likert (0,1,2,3) scale to analyse the data from the Chalder Fatigue Questionnaire was included as part of the planned analysis in both the application and published protocol, but was included as a secondary outcome. As with the application there was no use of the terms “recovery” and “positive outcome”.

As a funder of the trial the MRC was a member of the Trial Steering Committee (TSC) in a non-voting capacity. Any changes to the trial protocol would have been discussed at the TSC and therefore the MRC would have received notification through this route. The minutes of the TSC meetings do refer to discussions around the detail of the protocol and analysis plan, but again do not mention the terms “recovery” or “positive outcome”.

I hope that you find this information useful. If you are not satisfied that this response has been handled appropriately you may appeal using the MRC’s complaints procedure. Details are on the MRC website at: [4](http://www.mrc.ac.uk/about/information-s...). You may contact the MRC Complaints Officer at:

The Complaints Officer,
Medical Research Council,
14th Floor, One Kemble Street.
London,
WC2B 4AN.
email: [5](email address)

If you remain dissatisfied with the handling of your request or complaint, you have a right to appeal to the Information Commissioner at:

The Information Commissioner’s Office,
Wycliffe House,
Water Lane,
Wilmslow,
Cheshire,
SK9 5AF.
Telephone: 0303 123 1113.
Website: [6](www.ico.org.uk)
There is no charge for making an appeal.

Yours sincerely,

Rosa Parker

Corporate Information and Policy Manager
Corporate Affairs Group
Medical Research Council

www.mrc.ac.uk

Dear Medical Research Council,

Many thanks for your reply.

As you point out, Primary and Secondary Outcome Measures were altered or removed from the published Protocol.

When did the MRC know about this? The date please.

You remark "minutes of the TSC meetings do refer to discussions around the detail of the protocol and analysis plan" What are the dates of these discussions?

I seems from your reply that it is not clear whether the researchers or TSC officially informed the MRC about changing the Protocol, but it was taken as a 'given' because a representative of the MRC was on the TSC. Presumably this was Dr Perkins. When did she notify or record these changes in MRC records in accordance with MRC policy?

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The Trial Steering Committee discussed the protocol in detail at a meeting held on 22 April 2004.

The Trial Steering Committee joined a meeting of the Analysis Strategy Group held on 04 September 2009. It was at this meeting that the change
in the analysis of the Chalder Fatigue Questionnaire was discussed and agreed i.e. the planned secondary outcome measure of the scale using the Likert (0,1,2,3) scale would become part of the primary outcomes instead of the bimodal (0,0,1,1) scale.

The MRC considers that attendance at a meeting of the Trial Steering Committee and/or receipt of a copy of the minutes to be notification of any changes made.

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London,
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Rosa Parker
Corporate Information and Policy Manager
Corporate Affairs Group
Medical Research Council

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