Health Research Authority

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Rt Hon Norman Lamb MP
Science and Technology Committee
House of Commons
London
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29 January 2019

Dear Mr Lamb,

Re: The PACE trial and the Committee's inquiry on Research Integrity

When I gave evidence to the Science and Technology Committee inquiry on Research Integrity last year, Carol Monaghan MP took the opportunity to ask me about the PACE trial with regards to research transparency. After the event I also received further particulars through communications from campaigners who followed up with me directly. Since then the Health Research Authority (HRA) has examined this study in detail, and I am now writing to you and the Committee to update you on our assessment. We have set out some useful background below and addressed three points in turn. We also note that some of the criticisms of the PACE trial which have been brought to our attention are outside our regulatory remit and so we are not in a position to comment on them.

Background

The PACE trial was an evaluation of the therapies that were recommended by NICE at the time that the study was proposed, with the caveat that the evidence base at this time was weak. It was therefore appropriate for a well-designed trial to seek to improve the quality of evidence to be proposed. The selection of treatment options for the study was determined by current practice; this was not a trial seeking to promote a new therapy. One area of contention is the use of the Oxford diagnostic criteria for inclusion in the study. This was the definition that was in use in clinical practice in the places where the participants were recruited, and so it was appropriate to use this for an evaluation of the therapies in the UK. Whether the definition used in the USA is preferable for the future is not of regulatory concern but would be relevant to consideration of future trials.

While the quality of the trial design has been challenged, it has not been discredited. Criticisms have been made and responded to by the investigators. The issues remain debated but there has been no retraction of papers. In relation to one paper (not the one containing the main results) an 'expression of concern' has been registered by the publisher, along with the authors' response. It would not be appropriate for the HRA to seek to resolve these debates about the quality of the study. Discussion of the meaning and robustness of results is how science is expected to proceed.

Our concern as a regulator is whether the study was properly approved by the Research Ethics Committee (REC). The main funder was the Medical Research Council whose peer review processes would be regarded as robust. It was appropriate for the REC to rely on that scrutiny as assurance of the scientific quality.

The continuing debate about the design of the study is not an indication that it should not have been approved, but if there was a general and consistent view that it was of poor scientific quality then it would give us cause for concern. This is not the case in relation to PACE. A review of the reception of the study shows indications that the science is sound, as well as evidence of concern. The results of the trials were published in high impact journals with peer review processes that would generally be regarded as robust (though not infallible). The robustness of the PACE trial has been considered in a Cochrane review that classified it as high quality. This was also challenged by critics, and the author of the review responded to those criticisms. It would be as inappropriate for the regulator to disregard these indications that the trial was of high quality as to ignore the criticisms that have been expressed. The range of views suggests that the debate needs to be continued, not constricted by regulatory action.

Overview

There were many elements of good practice in the conduct of the PACE trial that were ahead of contemporary regulatory requirements in relation to transparency. In particular,

- The trial was co-designed with a patient group.
- The trial was prospectively registered in ISRCTN on 22 May 2003. Contrary to some claims, this is prior to patient recruitment, which commenced in March 2005.
- The protocol was made publicly available from March 2007, enabling critics to comment via open peer review. The trial investigators responses to those criticisms are in the public domain.
- The statistical analysis plan was made publicly available, enabling comparison of the planned analysis with the published results. This is an important safeguard against risks that only positive results are published as it exposes changes and requires them to be justified. The plan was fixed in 2010, prior to database lock, submitted to the journal Trials in 2012 and published in 2013.
- The researchers have made information available for secondary analysis to those who are prepared to confirm their adherence to conditions in relation confidentiality requirements.

In the light of the concerns that have been raised by the Committee and in the Westminster Hall debate held on 21 June 2018, we have specifically examined three matters that relate to our regulatory remit. These are conflicts of interest, the making of data available for further analysis, and the appropriateness of changes to outcome measures. In this, we have benefited from concerns being raised with us by critics and documentation to which they have pointed us. We have also drawn from publicly available documentation and reviewed the records that we have inherited from our predecessor organisations (although these are not comprehensive).

Conflicts of Interest

Critics of the trial raise concerns that there was a failure to comply with the standards contained in the Declaration of Helsinki over the disclosure of conflicts of interest. One issue concerns the involvement of the Department of Work and Pensions (DWP) as one of the funders. The information that all participants received included this fact and we therefore conclude that this was transparent and must be taken as acceptable to those who chose to take part. Concern has also been raised about potential conflicts of interest on the part of investigators. The trial protocol notes more extensive 'competing interests' than were included in the Patient Information Sheet (PIS). The differences concerned the advisory roles of the researchers. These were noted in the protocol but the PIS records only the sources of funding.

This process was probably consistent with the contemporary understanding of when a 'competing interest' should be regarded as a 'conflict' of interest for the purposes of research ethics approval. This was understood at the time as a matter of personal benefit. The WHO (2011) definition is:

Conflict of interest: In the research context, scientists have a conflict of interest if they stand to achieve personal gain (money or the equivalent) by failing to discharge professional obligations, either to protect the welfare of participants or to uphold the integrity of the scientific process.

Critics of the trial have raised concerns that the researchers were conflicted because they were advocates for the therapies that were being investigated. From the evidence we have identified, this is based primarily on presentations they have given to insurance companies and to government. However, it should be noted that the treatments that were being discussed were the therapies that NICE recommended, so all expert advisors would have been expected to explain them to such bodies. It is not clear what 'personal gain' the investigators stood to make from the trial and, in particular, it is not clear how any remuneration they received from advisory roles would have been different depending on the outcome of the trial.

Given that the REC was aware of the competing interests that are regarded by some critics as giving rise to a conflict of interest, and that they approved the trial including the PIS, it is not appropriate to criticise the researchers for non-disclosure. However, this is an area where greater clarification of expectations would be helpful. The Academy of Medical Sciences has recommended that further consideration and guidance is needed in relation to problems of conflicts of interest. The Health Research Authority is currently revisiting its guidance in this area.

Availability of data for secondary analysis

There has been criticism of Queen Mary University of London (QMUL) as a result of a successful tribunal challenge to their rejection of a request made under the Freedom of Information Act (FOI). However, the full picture shows that the general approach was to release data responsibility. Any suggestion that the researchers have routinely denied access

to prevent proper analysis of the data is not consistent with our enquiries, and to focus solely on the tribunal decision that went against QMUL gives a misleading picture.

Analysis of FOI requests to QMUL in relation to the PACE trial indicate that data was released in response to 9/21 of FOI requests where it was held. A search of the Information Commissioner's Office (ICO) decisions has identified 14 relating to the PACE trial. In 10 of those the ICO accepted the QMUL position. QMUL appealed in two of the four cases in which the ICO determined that data should be released. The tribunal overrode the ICO decision in the first case but upheld it in the second, in which it concluded that anonymized patient level data could be disclosed without breaching confidentiality. This pattern shows that judgments are required on how to draw the line between protection of participants' privacy rights and the transparency of research data. In all but three of the 21 cases, the judgment made by QMUL was vindicated. This suggests that the QMUL and the triallists' approached the issue of transparency of data for analysis responsibly.

However, looking forward, there is a need for further clarification of transparency requirements, particularly as a result of the second tribunal decision, in which a number of arguments raised by QMUL were rejected. The HRA will take this forward as part of its work on transparency. It is entirely proper that trials are debated in the scientific community. One of the objectives of transparency regulation is to ensure that this is possible.

Alterations in the outcome measures used

The final issue concerned changes to eligibility criteria and outcome measures. We do not hold a complete record of correspondence and proceedings in relation to the study, which was considered prior to the establishment of the HRA. However, we have been able to confirm that changes to the eligibility criteria and the supplement of the categorical outcome scores by measures of improvement were approved by the relevant research committees as 'substantial amendments'. We have not seen evidence that outcome measures were changed in order to achieve a specific outcome. The decisions were made prior to analysis being carried out, as reported in the published statistical analysis plan and corroborated by the minutes of the joint meeting of the Trial Steering Committee and Data Monitoring and Ethics Committee on 10 September 2010. As both the protocol and the statistical analysis plan were placed in the public domain, any differences between initial plans and published results can be identified and their significance debated. The changes were also openly reported in the main Lancet paper of 2011. This seems to us to be an example of the benefits of transparency.

Summary

Our review suggests that the PACE trial exceeded expectations in its transparency when judged against contemporary expectations. It was registered prior to recruitment commencing, something which is expected of all researchers but, as the Committee has pointed out, is not always met. The investigators made the protocol public and subject to open peer review. They also published the statistical analysis plan. We commend the investigators of PACE for recognising the importance of transparency by acting on good practice recommendations for publication on protocols and the statistical analysis plan even though they are not regulatory requirements. These are practices that we would want to encourage and this openness has enabled proper scientific debate about the results of the trial and how they should be interpreted.

We have reviewed the concerns about conflicts of interest that were raised with me at the Committee and have found that the declarations were consistent with the contemporary standards. The REC was aware of the material issues and approved the terms in which the involvement of DWP as a funder was communicated to participants. We have concluded that there is no basis for individual criticism here, but that we should work with stakeholders to consider whether expectations for disclosures should be redefined for the future to meet current participant expectations. This work is currently underway.

We have therefore concluded that there are no regulatory concerns about the conduct of the investigators in relation to these issues. However, we are grateful to the Committee for drawing out attention to the PACE trial as it has raised a number of matters that will inform our future work on transparency.

Yours sincerely

Professor Sir Jonathan Montgomery
Chair