Questions submitted by Professor Malcolm Hooper to The Countess of Mar re: the PACE Trial for the attention of the Minister of State for Universities and Science, the Rt Hon David Willetts MP, who is responsible for the Medical Research Council

7th May 2012

Clinical trial registration has become a pre-requisite for publication in reputable medical journals, leaving non-compliant trial "findings" with uncertain status.

Given that lack of transparency in clinical trial conduct, publication bias, non-adherence to the published Protocol, selective reporting bias and the omission of important data from published trials that can lead to erroneous recommendations for treatment are serious problems in medical research, and that clinical trials registration is essential to avoid these problems:

1. Will the Minister confirm that failure to comply with proper clinical trial registration undermines public confidence in medical research, and that it is not acceptable for a publicly-funded trial to be improperly registered

2. Will the Minister therefore ascertain and explain why the PACE Trial is incompletely registered in the ISRCTN (International Standardised Random Controlled Trial Number) Register (the PACE Trial registration being ISRCTN54285094), given that accurate registration, including the recording of all changes in procedure from the point of registration onwards, is required as a condition for publication in reputable journals

3. Will the Minister ascertain from the Editor-in-Chief of The Lancet and explain why an article reporting selective outcomes of the PACE Trial was deemed acceptable for publication in The Lancet (The Lancet: 2011, 5th March: 377:823-836), when the Editor-in-Chief, Dr Richard Horton, is a member of the International Committee of Medical Journal Editors (ICMJE) which "*requires, as a condition of consideration for publication, registration in a public trials registry"* and that such registration must be completed in all 20 fields in the WHO minimal data set and will be considered inadequate if it has missing fields or fields that contain uninformative terminology, as is the case with the PACE Trial, where changes from the approved Protocol have not been recorded in the Register as required: previously logged information has been removed from the trial record; fields are missing entirely and fields contain uninformative terminology, even though Current Controlled Trials (CCT), a body

which includes representatives from both the MRC and the DoH, states: "*CCT does not remove information from a record, or overwrite previous information, but will instead add any updated information, along with a date stamp to show when changes were made to the trial record*"

4. Will the Minister confirm which disease or condition was being studied in the £5 million PACE Trial that was co-funded by the MRC, the DoH, the DWP and the Scottish Chief Scientist's Office and which purported to be studying "CFS/ME" (CFS being a synonym for ME and classified in the WHO ICD-10 at G93.3), yet the Chief Principal Investigator (PI), Professor Peter White, has confirmed in writing that the PACE Trial did not purport to be studying ME, even though the trial documentation refers to "CFS/ME" and ethical approval and funding were granted on the basis that the PIs would be studying "CFS/ME"

5. Will the Minister ascertain and explain why the PACE Trial sponsor was changed from The MRC Clinical Trials Unit to The Medical Research Council and then to the Queen Mary University of London (UK) and why these changes are not recorded in the Register (for the record, the sponsors of the PACE Trial are referred to in The Lancet article as being the Medical Research Council, the Scottish Chief Scientist's Office, the Department of Health in England and Wales and the Department for Work and Pensions)

6. Further, given that the WHO International Clinical Trials Registry Platform (whose Scientific Advisory Group includes The Lancet's Dr Richard Horton) that is linked to the major ISRCTN Register requires that those responsible for completing the Register "*Must not have conflicts of interest over which trials or trial information to register"* and must "*Collect full Trial Registration Data Set"*), will the Minister clarify if the change of sponsor was related to a conflict of interest on the part of one of the UK Directors of the ISRCTN responsible for the registration and tracking of changes (Dr Chris Watkins of the MRC Neurosciences and Mental Health Board, on which two of the PACE Trial PIs, Professors Peter White and Trudie Chalder also served, as Watkins authored the 2003 MRC "CFS/ME Research Strategy" that recommended further research into the psychosocial interventions graded exercise therapy [GET] and cognitive behavioural therapy [CBT] as opposed to any biomedical studies into ME/CFS and his support for the PIs is a matter of record)

7. Will the Minister ascertain the real reason and clarify why the scoring instruments were changed once the PACE Trial was underway (ie. on entry, participants' results were scored using one measurement scale and on completion were scored using another measurement scale) and why this change is not recorded in the Register, since many informed people find the PIs' proffered explanation to be unconvincing *("we changed the original bimodal scoring of the Chalder fatigue questionnaire (range 0–11) to Likert scoring to more sensitively test our hypotheses of effectiveness")*, given that in the FINE Trial (a sibling of the PACE Trial

wholly funded by the MRC), when scored bimodally the interventions did not achieve statistical significance, but when a post-publication *post-hoc* analysis was carried out using Likert scoring, it was possible to demonstrate a clinically unimportant but statistically significant effect

8. Will the Minister ascertain and explain why the recovery statistics and other outcomes that were defined in the published Protocol (such as the number of PACE Trial participants who have returned to gainful employment) have not been published, given that such outcomes are of considerable public interest and are of importance to the funders (the PACE Trial being the only clinical trial that the DWP has ever funded and it did so on the understanding that the interventions would return participants to employment)

9. Will the Minister ascertain from the Chief PI why he lowered the definition of "normal" physical function: is the Minister aware and content that in 2002, the Chief PI calculated the "normal range" for physical function at the outcome of the PACE Trial to be an SF-36 (physical function) score of 75 or above out of 100, yet when he performed the same calculation in 2011 for publication in The Lancet, he had re-calculated this figure to be just 60 out of 100, which is five points lower than the score required to enter the trial and is 15 points lower than his written commitment given in 2006 to the West Midlands Multi-Centre Ethics Committee (MREC) that the score required for a "*categorical positive outcome"* would be 75, thus *"reasserting a ten point score gap between entry criteria and positive outcome*", and why these changes are not recorded in the Register

10. Will the Minister specifically request an explanation from the Chief PI why both primary outcome figures (fatigue and physical function) were changed so that they were lower than those required forentry to the trial (ie. a participant could actually deteriorate during the Trial yet still fall within the PIs' amended "normal range" at the completion of the Trial), and how such a situation can be regarded as good scientific practice

11. In the light of this, will the Minister call for an urgent independent re-analysis of the raw data in order to know the outcomes as listed in the published Protocol

12. Will the Minister confirm what steps he proposes to take to rectify this apparent scientific fraud that is already causing iatrogenic harm to patients with the neuroimmune disorder ME, since the Chief PI is on record in his keynote address at the BACME conference held on 14th-15th March 2012 as stating that "pacing" (ie. living sensibly within one's physical limits) should be removed from the clinicians' lexicon, as referring to the PACE Trial as a "*magnificent achievement"* and as urging the extensive use of the interventions CBT and GET

13. Given the non-conformity with the ISRCTN Register requirements, will the Minister clarify the MRC's legal position as a co-funder of the PACE Trial regarding the subsequent reliance by NICE and the DWP on the outcome as reported in The Lancet which has such potentially harmful clinical implications for those with ME due to the demonstrated immune and cardiovascular dysfunction

14. Since no recovery statistics have been published, is the Minister aware of the misrepresentation of the PACE Trial outcome and false interpretation of the reported outcome such as those by Bleijenberg & Knoop who asserted that about 30% had "recovered" (Lancet 2011: doi:10.1016/S0140-6736(11)60172-4) and by Collin and Crawley et al who compounded this error by stating: "*Evidence from a recent evidence* (sic) *trial of cognitive behavioural therapy and graded exercise therapy indicated a recovery rate of 30-40% one year after treatment"* (BMC Health Services Research 2011:11:217)

15. Does the Minister agree that without full trial information in the Clinical Trials Register, readers cannot fairly assess the validity of the reported PACE Trial findings because changes which might alert Register users to possible problems within the conduct of the PACE Trial have not been recorded or are recorded in a way that is misleading, thereby undermining the rationale of trial registration.