Myalgic Encephalomyelitis / Chronic Fatigue Syndrome and Fibromyalgia:

additional considerations for the MRC in relation to the PACE trials

Margaret Williams

5th January 2005

Further to previous observations on the clear differences between ME/CFS and fibromyalgia already provided for the MRC's consideration, two additional points may be of relevance.

In 1994, the British Medical Journal published information from Dr Darrel Ho-Yen, a well-known and respected virologist and researcher into ME then at Raigmore Hospital in Scotland, who stated the following: "The distribution and number of tender points in fibromyalgia are different from the chronic fatigue syndrome, **and the management of the two conditions is different. Patients with (ME/CFS) should be advised not to increase their activities gradually until they feel 80% of normal, whereas patients with fibromyalgia may benefit from a regime of increasing activity"** (BMJ 1994:309:1515).

In 1999, Professor Leonard Jason and colleagues published an updated US case definition for (ME)CFS which seems to have received little attention from certain UK psychiatrists who are on record as believing that "CFS/ME" is a psychosocial disorder and who regard the many abnormalities present in the disorder as inconsequential. This 1999 US case definition makes two points of particular and current relevance to the MRC PACE trials:

"If a person with chronic fatigue syndrome specifies a large number of physical problems caused by this illness, these physical problems might also make the person eligible for a diagnosis of somatization disorder, depending upon the accuracy of the diagnostician. Fibromyalgia Syndrome (FMS) and Multiple Chemical Sensitivity (MCS) **represent additional illnesses of interest where issues of diagnostic accuracy are concerned".** (JCFS:1999:5:3-33).

In the interests of evidence-based medicine, those involved with the MRC PACE trials may wish to reflect upon the available evidence, given that long-established elementary rules of procedure demand that those undertaking research are normally required before proceeding to define the proposed topic and to produce a comprehensive review of the relevant literature: only by so doing can they place themselves in a position to ensure that their own prospective contribution represents a potentially useful and original development of knowledge that is based squarely on the foundations of existing knowledge.

By proposing to proceed as if a substantive body of mainstream knowledge did not exist, those involved lay themselves open to suspicions of ignorance and / or disingenuousness, or even frank intellectual dishonesty.

As has been previously noted, investigators are, of course, always at liberty to take issue with established knowledge, but if they wish to do so legitimately and credibly,

they need to provide a reasoned critique of each tenet of established knowledge from which they propose to depart and to provide convincing arguments to show that the proposed research strategy will move understanding and knowledge along and will not simply reinforce existing confusion.

For convenience, information already provided for the MRC PACE trial investigators about the most recognised differences between ME/CFS and FM is reproduced and summarised here:

In respect of the MRC CFS trials, there are known and established differences between FM and ME/CFS and many believe that the FM community and the ME/CFS community have a right to know why patients suffering from both disorders are to be amalgamated in the MRC trials that claim to be studying "CFS".

Likewise, an explanation is required as to why GPs are suddenly to be offered financial incentives to identify and refer people with FM to the new CFS centres specifically so that such patients can be entered into the MRC studies of "CFS".

It is a matter of record that Whiting et al expressly excluded FM studies from the systematic review of the literature that was commissioned by the Policy Research Programme of the Department of Health and carried out by the Centre for Reviews and Dissemination at the University of York for the CMO's Working Group on CFS, the results of the systematic review being intended to underpin the conclusions of that report (namely that cognitive behavioural therapy, including graded exercise regimes, is the management of choice for patients with chronic fatigue syndrome). The systematic review is unequivocal: **"Studies including patients with fibromyalgia were not selected for the review"**; why, therefore, and on what evidence, was it decided to include patients with FM in the subsequent MRC trials of CBT on a CFS population? (*see* Interventions for the Treatment and Management of Chronic Fatigue Syndrome. Penny Whiting et al. *JAMA 2001:286:11:1360-1368*).

Of foremost significance is the fact that fibromyalgia is classified as a distinct entity in ICD-10 at section M79.0 under Soft Tissue Disorders and it is not permitted for the same condition to be classified to more than one rubric, since ICD categories are mutually exclusive.

The literature itself is quite clear about this distinction, stating that up to 70% of those with ME/CFS have *concurrent* FM, and those who have both FM *and* ME/CFS have worse physical functioning than those who have ME/CFS alone.

Some illustrations from the literature make these distinctions clear:

1991: in spite of some overlap, FM and ME/CFS do not represent the same syndrome. (Primary fibromyalgia and the chronic fatigue syndrome. AJ Wysenbeek et al *Rheumatology Int 1991:10:227-229*)

1996: "fibromyalgia appears to represent an additional burden of suffering amongst those with (ME)CFS" (Fibromyalgia and Chronic Fatigue Syndrome – similarities and differences. Dedra Buchwald and Deborah Garrity. *Rheum Dis Clin N Am 1996:22:2:219-243*)

1997: levels of somatomedin C are lower in FM patients but higher in ME/CFS patients (Somatomedin C (insulin-like growth factor) levels in patients with CFS. AL Bennett, AL Komaroff et al. *J psychiat Res 1997:31:1:91-96*)

1998**:** "recent studies suggest that (co-existent FM and (ME)CFS) may bode much more poorly for clinical outcome than CFS alone. In contrast to (significantly) elevated CBG (cortisol binding globulin) levels in patients with CFS, no differences were observed in FM patients. Differences in secretion of AVP may explain the divergence of HPA axis function in FM and (ME)CFS" (Evidence for and Pathophysiologic Implications of HPA Axis Dysregulation in FM and CFS. Mark A Demitrack and Leslie J Crofford. *Ann New York Acad Sci 1998:840:684-697*)

1998: there is no evidence for elevated Substance P in patients with ME/CFS, whereas levels are elevated in patients with FM (CFS differs from FM. No evidence for altered Substance P in cerebrospinal fluid of patients with CFS. Evengaard B et al *Pain 1998:78:2:153-155*)

2001: patients with FM are *NOT* acetylcholine sensitive (Investigation of cutaneous microvascular activity and flare response in patients with fibromyalgia. AW Al-Allaf, F Khan, J Moreland, JJF Belch. *Rheumatology 2001:40:1097-1101*)

2004: patients with ME/CFS *ARE* acetylcholine sensitive (Acetlycholine mediated vasodilatation in the microcirculation of patients with chronic fatigue syndrome. VA Spence, F Khan, G Kennedy, NC Abbot, JJF Belch *Prostaglandins, Leukotrienes and Essential Fatty Acids 2004:70:403-407*)

2003: endothelin-1 is *RAISED* in fibromyalgia (Increased plasma endothelin-1 in fibromyalgia syndrome. Pache M, Ochs J et al *Rheumatology 2003:42:493-494*)

2004: endothelin-1 is *NORMAL* in ME/CFS (Plasma endothelin-1 levels in chronic fatigue syndrome. Kennedy G, Spence V, Khan F, Belch JJF *Rheumatology 2004:43:252-253*)

Consultant rheumatologists who have sufficient experience with both syndromes have observed clinically that in FM, the muscle pain is helped by gentle stretching and exercise, whereas in ME/CFS, exercise makes muscle pain worse.

If the Oxford criteria are to be used for the MRC "CFS" trials, on what logic (other than a pre-determined agenda) can patients with FM, a completely separate disorder, be intentionally included from the outset?

Is the MRC entirely content that the PACE trial proposal also states "**Those subjects who also meet the criteria for "fibromyalgia" will be included"**, given that FM is classified by the WHO as a quite separate disorder from ME/CFS, with a discrete biomedical profile that is entirely distinct from that found in ME/CFS?

Importantly, on 3rd June 1998, Baroness Hollis from the then Department of Social Security sent a letter to Lindsay Hoyle MP (reference POS(4) 3817/88) which says "The Government recognises that fibromyalgia syndrome (FMS) is a condition which can cause a wide variety of disabilities from mild to severe. In some cases it can be a

very debilitating and distressing condition. People with FMS who need help with personal care, or with getting around because they have difficulty in walking, can claim Disability Living Allowance to help with meeting related expenditure". From this letter, it is clear that Government already recognises fibromyalgia as a distinct entity.

Further, in the CMO's UPDATE of August 2003 (a paper communication from the CMO sent to all doctors in England) entitled "Improving Services for Patients" there is an item called "Fibromyalgia – A Medical Entity". This means that the CMO considers fibromyalgia to be a separate, stand-alone medical entity (and the fact that it is designated a "medical" disorder means that it is not considered to be "psychiatric" disorder).

How can the deliberate inclusion of patients with fibromyalgia in trials that purport to be studying "CFS" not result in skewed and meaningless conclusions when the patients being entered in the PACE trials are, from the outset, not clearly defined?