P2P Comments from NA Wright

General Statement:

The P2P process is to be welcomed as a determined attempt to break the multiple log jams, both bureaucratic and scientific which so gravely hinder progress in understanding and treating ME/CFS, and in providing ongoing support for patients. Despite some inadequacies even as written the Draft Report stands as a unique indictment of the state of medical science as it addresses (or more accurately does not) ME/CFS.

Comments on the Draft Executive Summary

Lines 2, 3 and 4: The identification of fatigue as being so notable that it is deserving of specific identification rather than equal listing with other symptoms, adheres to an accepted prioritisation that is not supported by evidence. Patients report a range of symptoms none of which has been shown to be more uniquely disabling than any other. It would be desirable if the P2P could break with the scientifically unsupported convention of placing fatigue as the single most important identifier, and simply acknowledge the multiplicity of disabling symptoms without giving pre-eminence to any one. Indeed the document recognises this very point at Lines 58 and 95 !

Line 5: While a gender differential seems likely, the phrase 'mostly women' lacks accuracy and as the report acknowledges (Line 72), epidemiological studies are lacking, consequently no one knows what the gender differential actually is. The final report should more properly refer to a poorly quantified gender differential, rather than something that might imply orders of magnitude differences in the numbers of males and females affected.

Line 38 et seq: Guidelines for research (Oxford criteria *sic*) published in 1991 are exceptionally identified as lacking validity despite their only limited use. The inclusion of this specific derogation in the document, without reference to the separate needs of research and of clinical practice and the various failings of other case descriptions and criteria proposed for ME/CFS, seems to bespeak a certain confusion that runs through the document.

No single set of criteria will serve all research purposes and the needs of clinical practice can be at great variance to the requirements of a single area of research. It is a failing of the Draft document that these issues are not clearly delineated and the authors have evidently struggled with the problem of pinning down ME/CFS as a single entity demanding a single definitional categorisation. The authors might perhaps consider this issue more fully before publishing their final report, particularly the probability that what has conventionally been conceived of as a single ME/CFS 'disease' is actually a multiplicity of disease processes each of which is expressed in variable or absent ranges within individuals and evidenced variably across the patient population. Looking for the perfect criteria would be a serious diversion of effort, if what is actually under examination are multiple illnesses of occult causation, all producing a common but broad

suite of symptoms. It is the case that many patients have long placed their hope in the use of better criteria for both diagnosis and research, however this hope appears based in large measure on a fairly simplified assessment of what ME/CFS must actually be, both in causation and in continued organic function. At this stage of understanding it would be misguided to pursue the ideal of a perfected case definition at the cost of continued well directed research. [further commentary at Line 105 below]

Line 99 et seq: The document usefully identifies the need within research, to distinguish between ME/CFS and ME/CFS with co-morbidities and between subjects who have exclusionary conditions, this is an issue which commands elaboration in the final document. The inadequacy of research cohorts is a symptom of a much wider problem of poor or wrong treatment of ME/CFS patients with co-morbidities and also the very profound problem of wholly wrong treatment in cases where an entirely treatable condition is misdiagnosed as ME/CFS. [UK data: *J R Coll Physicians Edinb* 2010; 40:304–7doi:10.4997/JRCPE.2010.404 and JRSM Short Rep. Jan. 2012; 3(1): 4.] The authors do, at Line 142 acknowledge misdiagnosis of other diseases for ME/CFS, however the reverse is also important to acknowledge.

Line 105: The document identifies "a clear case definition with validated diagnostic tools" as needed before studies can be conducted. This might be considered a case of putting the 'cart before the horse', where the limitations of Fukada, Oxford etc are merely repeated with a better line up of symptoms in the expectation that a well defined symptomology will lead the way to accurate illness definition. To demand a perfected case definition before research can progress may very well place a perpetual inhibition on research as each symptom dissolves into nebulousness under the demand of scientific certainty. The document notes "fatigue, post exertional malaise, neurocognitive deficit, and pain" but gives no basis for assuming that these terms are relatable to any distinct disease processes in ME/CFS. Rather than looking for research cohorts that solely meet the assumed ideal case definition, a more pragmatic approach may be to require that all ME/CFS research accurately records participant symptomology. ME/CFS may be multiple diseases and research focussed on an overly closely characterised symptomology may actually inhibit progress, rather than support it.

Line 139 et seq: The text again appears to conflate the demands of research with the demands of clinical support for patients and is a major failing of the Draft document, some additional clarity needs to be brought particularly to this section. There are many good points made all the way through to Line 177, but their application to either research or to clinical circumstances, needs to be specified.

Line 213: "Investing in bench-to-bedside to policy research"; patients might also say that

'investing in bedside–to-bench' policy research would pay dividends – patients being a potential source of profound policy insights.

Closing Comment.

There is much to be commended in the Draft document. The observations provided here are offered in the hope that they support the production of a stronger final document. The NIH has embarked on a process that could bring about a step change in the way a neglected illness (or indeed illnesses) is dealt with. Thank you for accepting this submission from a non US resident; scientific endeavour is increasingly international and it is to be hoped that the NIH's initiative will be emulated by its counterparts across the developed world.