From: [NICE employee]
Sent: 24 March 2017 15:05
To: [topic expert]; [topic expert]; [topic expert]; [topic expert]; [topic expert]; [topic expert]
Cc: [topic expert]; [NICE employee]
Subject: Request for additional expert opinion on diagnostic criteria for CFS/ME

Dear all,

We would appreciate your feedback on some issues discussed below – please could you provide any responses to Qs 1 & 2 **by Sunday 9 April**. This is a request for some additional input to the process. The key documents for you to review will be circulated in a few weeks' time as explained in my email yesterday.

[redacted] (out of scope)

In 2015, NICE was made aware of 3 reports from the USA containing information relating to diagnosis that may have implications for the guideline:

- 1. AHRQ (Agency for Health Research and Quality) (2015) Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Evidence Report/Technology Assessment No. 219 (July 2016 addendum)
- 2. IOM (Institute of Medicine) (2015) Beyond myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an illness
- 3. Recommendations from the Health and Human Services Chronic Fatigue Syndrome Advisory Committee (2015)

NICE's initial assessment of these papers can be seen in the table below.

Notably, 2 of these reports requested a 2-5 year period going forward in which the validation and development of new criteria should take place. Since these reports published in 2015, we have not yet found any reported activity of validating the proposed diagnostic criteria.
Q1: Are you aware of further work to validate the new diagnostic criteria proposed in these reports?

Q2: We would also appreciate your thoughts on the current status of diagnostic criteria, in CG53 and elsewhere, in light of these reports. For example:

- **Is there a sense in the community that there is a need for changes to current diagnostic practice?**
- **Are there concerns about the inclusion criteria of trials in CFS (such as those used to develop CG53 originally, and more recent studies)?**

Summary of evidence	Impact on guideline recommendations
1. The AHRQ report concluded that none of the current diagnostic methods have been adequately tested to identify patients with ME/CFS when diagnostic uncertainty exists.	Changes to diagnostic criteria might have implications for the applicability of any research used to inform the current guideline. This report did not recommend a particular change. There is therefore no clear impact on the guideline recommendations.
2. The IOM report considered the diagnostic criteria for CFS/ME and proposed the following:	The proposals differ from the recommendations for features suggesting the possibility of ME/CFS in CG53 and from the approach to diagnosis in CG53. It is likely that

Diagnosis requires that the patient have the following 3 symptoms: 1. A substantial reduction or impairment in the ability to engage in preillness levels of occupational, educational, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest, 2. Post-exertional malaise,* and 3. Unrefreshing sleep* At least one of the two following manifestations is also required: 1. Cognitive impairment* or 2. Orthostatic intolerance The report additionally recommended that ***'A multidisciplinary group should reexamine the diagnostic criteria set forth in this report when firm evidence supports modification to improve the identification or care of affected individuals. Such a group should consider, in no more than 5 years, whether modification of the criteria is necessary'*** * Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.	the proposed criteria would also differ from the inclusion criteria for studies of interventions for people with ME/CFS. It is difficult to predict the effect this might have on the recommendations in CG53. However, it is worth noting that this is a proposal, and must be interpreted alongside the subsequent recommendations of the HHS Chronic Fatigue Syndrome Advisory Committee.
3. The report of the HHS Chronic Fatigue Syndrome Advisory Committee made a number of recommendations for a US audience on the need for further research in this field, particularly around • biomarkers and objective diagnostic tests • gaps in basic, translational, clinical and epidemiological research to improve the understanding of the condition(s) • research on treatments for people meeting newly proposed diagnostic characteristics • standardised assessment and measurement tools	If the recommendations of the report are followed, the proposed diagnostic criteria will have been evaluated by the end of 2017. It may be too early to try to interpret the implications of the proposed changes until then. Noting that the Committee recommendations differ from the proposal made by the IOM, it seems quite possible that further changes may occur as a result of validation. One of the recommendations on treatment and care called for a "Declaration that the disease is not the result of fear-based avoidance of activity and that cognitive behavioural therapy (CBT) and graded exercise therapy (GET) for this purpose are inappropriate". CG53 recommends individualised use of these

The Committee also made some amendments to the proposed diagnostic criteria in the IOM report, including changing "unrefreshing sleep" to "sleep disturbances", added some features, expanded definitions, and **recommended a period of two years' validation of these.** The report made a number of recommendations regarding treatment and care, but also **recommended that clinical practice guidelines be developed.**	interventions, and does not recommend any particular assumptions about the cause of the disease. Therefore the impact of this statement is unclear.

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Response from topic expert 1

1. No, I am not aware of further work to validate the new diagnostic criteria proposed in the reports.

2. Diagnostic criteria are necessary because there are no diagnostic tests for CFS/ME, and no prospect of these in the foreseeable future. For this reason, in the scoping meeting prior to the development of CG53, there was a discussion on this. There was a very clear (near unanimous) consensus from the stakeholders who attended the meeting that supported the use of broadly defined diagnostic criteria. This was to allow the inclusion of the vast majority of sufferers, which more narrowly defined criteria would exclude. A corollary of this was that it allowed the inclusion of the majority of trials, which have typically used broad diagnostic criteria. I am unaware of any concerns about the inclusion criteria of trials in CFS, and indeed some trials have been analysed according to more than one set of diagnostic criteria.

I do not see any need to change the diagnostic criteria at present. From a clinical perspective, CG53 are pragmatic and useful criteria. In my clinical experience in a CFS/ME clinic over the 10 years since the guidelines were published, no concerns have ever been expressed by patients attending the clinic about the diagnostic criteria used in CG53. Given the incomplete nature of the proposals highlighted below, it would be difficult to justify any changes at present - particularly given the difficulties that may result from this, which include of course undermining the guidelines themselves.

Response from topic expert 2

I am not aware of further work to validate the proposed new criteria. I have attached below comments to yours in highlighted CAPITALS.

Summary of evidence	Impact on guideline recommendations
1. The AHRQ report concluded that none of the current diagnostic methods have been adequately tested to identify patients with ME/CFS when diagnostic uncertainty exists.	Changes to diagnostic criteria might have implications for the applicability of any research used to inform the current guideline. This report did not recommend a particular change. There is therefore no clear impact on the guideline recommendations. YES, THIS MAKES SENSE
2. The IOM report considered the diagnostic criteria for CFS/ME and proposed the following: Diagnosis requires that the patient have the following 3 symptoms: 1. A substantial reduction or impairment in the ability to engage in preillness levels of occupational, educational, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest, 2. Post-exertional malaise,* and 3. Unrefreshing sleep* At least one of the two following manifestations is also required: 1. Cognitive impairment* or 2. Orthostatic intolerance The report additionally recommended that ***'A multidisciplinary group should reexamine the diagnostic criteria set forth in this report when firm evidence supports modification to improve the identification or care of affected individuals. Such a group should consider, in no more than 5 years, whether modification of the criteria is necessary'***	The proposals differ from the recommendations for features suggesting the possibility of ME/CFS in CG53 and from the approach to diagnosis in CG53. It is likely that the proposed criteria would also differ from the inclusion criteria for studies of interventions for people with ME/CFS. It is difficult to predict the effect this might have on the recommendations in CG53. However, it is worth noting that this is a proposal, and must be interpreted alongside the subsequent recommendations of the HHS Chronic Fatigue Syndrome Advisory Committee. THIS IS ONLY A PROPOSAL. IT SEEMS TO ME UNLIKELY TO PROVE SUPERIOR TO CURRENT DEFINITIONS AND TO BECOME GENERALLY ACCEPTABLE IN THE FORESEABLE FUTURE. BUT IF IT WERE TO CONCLUSIVELY TURN PREVAILING DEFINITIONS OF CFS/ME ON THEIR HEADS, CURRENT GUIDELINES MAY NEED TO BE RE-WRITTEN.

* Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.	
3. The report of the HHS Chronic Fatigue Syndrome Advisory Committee made a number of recommendations for a US audience on the need for further research in this field, particularly around biomarkers and objective diagnostic tests gaps in basic, translational, clinical and epidemiological research to improve the understanding of the condition(s) research on treatments for people meeting newly proposed diagnostic characteristics standardised assessment and measurement tools The Committee also made some amendments to the proposed diagnostic criteria in the IOM report, including changing "unrefreshing sleep" to "sleep disturbances", added some features, expanded definitions, and **recommended a period of two years' validation of these.** The report made a number of recommendations regarding treatment and care, but also **recommended that clinical practice guidelines be developed.**	If the recommendations of the report are followed, the proposed diagnostic criteria will have been evaluated by the end of 2017. It may be too early to try to interpret the implications of the proposed changes until then. Noting that the Committee recommendations differ from the proposal made by the IOM, it seems quite possible that further changes may occur as a result of validation. One of the recommendations on treatment and care called for a "Declaration that the disease is not the result of fear-based avoidance of activity and that cognitive behavioural therapy (CBT) and graded exercise therapy (GET) for this purpose are inappropriate". CG53 recommends individualised use of these interventions, and does not recommend any particular assumptions about the cause of the disease. Therefore the impact of this statement is unclear. YES, THIS MAKES SENSE. SUPPORTING INCREASED ACTIVITY DOES NOT IMPLY FEAR-BASED AVOIDANCE, EVEN THOUGH THIS MAY BE THE CASE FOR SOME PATIENTS.

Response from topic expert 3

Q1: Are you aware of further work to validate the new diagnostic criteria proposed in these reports?

Not these criteria but there has been some work done on other criteria for example: https://www.ncbi.nlm.nih.gov/pubmed/25640602

Q2: We would also appreciate your thoughts on the current status of diagnostic criteria, in CG53 and elsewhere, in light of these reports. For example:

- **Is there a sense in the community that there is a need for changes to current diagnostic practice?**
- **Are there concerns about the inclusion criteria of trials in CFS (such as those used to develop CG53 originally, and more recent studies)?**

There is significant debate in the patient community (those that engage in debate on line/social media) about changing diagnostic practice.

There are concerns about recruiting using NICE guidance which is considered too broad and inclusive.

I would say: a) we recruit to all our trials using NICE criteria but obtain sufficient data to determine which patients would be classified as having CFS/ME using other research criteria such as the CDC (Fukuda) diagnostic criteria.

b) The scientific community agrees with the IOM recommendations on biomarkers but also recognises that recruiting patients to study biomarkers is best done using broad (permissive) criteria such as those recommended by NICE with sufficient phenotyping to determine those who fulfill other criteria and c) my patients are not aware of this debate and don't ever question which diagnostic criteria are used because they just want treatment.

Response from topic expert 4

None held

Response from topic expert 5

None held

Response from topic expert 6

1. I am aware of no further work on validation of diagnostic criteria in CFS/ME

2. It is difficult for anyone to state with a reasonable degree of certainty what the tensions are in diagnostic criteria.

I am suspect that there is a tendency in the USA to push towards an entirely biological explanation for the condition, whereas in the UK there is an increasing acceptance amongst patients and clinicians alike of a model that includes CFS/ME in the umbrella of functional neurological disorders, i.e. that it is an emotionally-driven disorder. This is highlighted in the statements from the HHS Chronic Fatigue Syndrome Advisory Committee:

“A priority should be placed on developing biomarkers and diagnostic tests... The field could be energized and diversified by creating opportunities for junior and new investigators to be involved… Current research has neglected many of the biological factors underlying ME/CFS onset and progression. Research priorities should be shifted to include basic science and mechanistic work that will contribute to the development of tools and measures such as biomarker or therapeutics discovery…"

In the UK I think we would see what the HHS CFSAC see as a failure to undertake rigorous research, more as a failure of the biological model to explain the condition adequately. However, I can understand that an alternative reaction to the failure of biological models to explain the condition is to try and define a subset of patients with the condition who appear to share a common biomarker. This approach has failed so far. For this reason I believe that at present the criteria originally adopted by NICE were adequate and that there is at present no compelling evidence of a need to change them.

Response from topic expert 7

1. I am not aware of any new funded work on the new criteria.

2. Since there are no exclusions, my concern is that these new criteria will include many more people with even more heterogenous conditions. This was one of the stated intentions because people with CFS/ME often have comorbidities but if they were used for research then there is a risk that aetiology, treatment etc will become even more unclear. I am particularly concerned that fear of exercise or activity is an exclusion as I have yet to meet a patient with any degree of disability from the condition who did not have at least some anxiety about over-exercising.

There is a lobby group of some patients and some clinicians to define a group of patients with CFS/ME that do not have mental health problems even though it is a condition that is likely to generate distress, fear for the future and despair. Apart from that it is not clear what these criteria achieve and there are no gold standards by which one set of criteria can be said to be better or worse than any other. If these criteria were to be employed for recommendations for assessment and management, then there would be very little that could be recommended in a new guideline because of the lack of research data using these criteria including whether or not these diagnostic criteria should be recommended. I do not

even know of a dataset in which to test these new diagnostic criteria because they all operated exclusion criteria that would not apply in the new diagnostic criteria.

I would continue with the existing NICE criteria in the absence any compelling empirical data to merit a change but acknowledge the concerns about diagnosis from some perspectives and the existence of these proposed alternative North American criteria that the developers of these criteria have also suggested require further research. The relative psychometric properties, merits and drawbacks of the new proposed criteria versus existing criteria could be a research recommendation in a new guideline. The NICE guideline might also suggest that new CFS studies record whether patients meet existing criteria and these alternative criteria so that a picture based on empirical data can emerge.