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DATE SENT: Sunday 6th June 2021

SUBJECT: Guideline in Development NG10091 ME/CFS: failure to take pertinent evidence into account

We are submitting this complaint after careful consideration, and with the recognition that the guideline in development holds the potential to be a considerable improvement on the existing guidance [CG53].

We appreciate that the draft for consultation has attracted a large volume of comment, and recognise the hard work of the guideline committee (GC) thus far.

However, the outcome of the efforts of any GC in large part hinge on the evidence put before them.

This complaint concerns evidence concerning the impact on patients of interventions, notably graded exercise and cognitive behavioural therapy, which has been screened out of consideration by NICE, and therefore not brought to the attention of the GC.

1. Analyses by Wilshire *et al.* of raw data from the PACE trial

These peer reviewed published papers analysing the raw data from the PACE trial have been excluded:

> Wilshire CE, Kindlon T, Matthees A, McGrath S. *Can patients with chronic fatigue syndrome really recover after graded exercise or cognitive behavioural therapy? A critical commentary and preliminary re-analysis of the PACE trial.* Fatigue: Biomedicine, Health and Behavior. 2017; 5(1): 43-56

> Wilshire CE, Kindlon T, Courtney R, Matthees A, Tuller D, Geraghty K *et al. Rethinking the treatment of chronic fatigue syndrome-a reanalysis and evaluation of findings from a recent major trial of graded exercise and CBT.* BMC Psychology. 2018; 6(1): 6

Despite their titles, these papers to not represent secondary or reanalyses as such, but analyses of raw data conducted according to the original PACE trial protocol.

In the letter to stakeholders sent December 2016 notifying commencement of a formal check on the status of CG53, NICE pledged to take this material into account: *"We have since been made aware of new information about the 2011 PACE trial, and we will also consider that in the review."*

Responding to the draft scope, many stakeholders raised concerns about the impact of exercise and CBT on ME/CFS patients. An assurance was given that the pertinent analysis would be "robust". The exclusion of the above papers is not in keeping with this pledge.

2. Patient reports: summative findings from surveys

One approach cited by NICE in connection with ensuring a robust analysis of the impact of graded exercise and CBT was the conduct of a call for evidence: *"To allow a robust analysis we also plan to review the published evidence on patient experience and conduct a call for evidence*

so that harms are identified and taken into account by the committee." [response to comments on the draft scope]

The ensuing call for evidence advised that survey findings would be taken into account: "*Qualitative studies evaluating focus groups and interviews and surveys will be considered for inclusion in the guideline".* As a result, a number of pre-existing surveys were submitted, as well as fresh surveys commissioned by the stakeholder organisations Forward-ME and #MEAction UK, respectively. Following submission in evidence, reporting of findings which involved summing responses - including regarding patients' experiences of graded exercise and CBT - and expressing them in percentage terms were considered inadmissible. This approach is particularly notable in respect of the findings of the Forward-ME Survey, given the origins of this piece of work:

> *This survey was commissioned by Forward ME following discussions between the Chair and Vice-Chair of the NICE Guideline Development Group, Members of Parliament and the Chair of Forward-ME about the lack of up-to-date data about providing additional patient evidence relating to long-term outcomes and harms following Cognitive Behavioural Therapy (CBT) and Graded Exercise Therapy (GET).*

This survey report was not amongst papers identified for full text evaluation *via* literature search. Having been submitted in the course of the call for evidence, only the qualitative reporting of open ended questions was considered admisible. In the event, *none* of the findings emerging - neither those expressed in qualitative or quantitative terms - feature in the synthesis of evidence on patient experiences presented to the GC in Evidence Review G.

This approach to exclusion is odd, given that such evidence *did* meet criteria for inclusion in the surveillance review *and* helped underpin the decision by NICE that a fresh guideline is required. From approximately 300 pieces of evidence highlighted to NICE by stakeholders during the review consultation, 13 met criteria for inclusion, including:

> Geraghty 2017: *Myalgic encephalomyelitis/chronic fatigue syndrome patients' reports of symptom changes following cognitive behavioural therapy, graded exercise therapy and pacing treatments: Analysis of a primary survey compared with secondary surveys* Journal of Health Psychology Vol. 24(10) 1318–1333; and
>
> Action for ME 2014: *Time to Deliver - Initial findings of 2014 survey*

Both publications were rated by NICE as having "potential" impact, described as follows:

> Geraghty 2017: "*Analysed data from a large cross-sectional patient survey (n=1,428) and compared findings with comparable patient surveys (n=16,665). CBT is of benefit to a small percentage of patients (8–35%); GET brings about large negative responses in patients (54–74%); while pacing is the most favoured treatment with the lowest negative response rate and the highest reported benefit (44-82%)."*
>
> Action for ME 2014: "*85% found pacing helpful, 12% found it made no change and 4% said their condition got worse (cf 54%, 34% and 12% for CBT and 48%, 19% and 24% for GET, respectively). Patients' value of treatments may not align with guideline recommendations."*

Neither have been taken into account In developing fresh guidance.

The import of patient survey findings (despite potential methodological limitations) was recognised almost two decades ago when the CMO's Working Group concluded: *"the data clearly indicate that the York review results do not reflect the full spectrum of patients' experience."* [Annex 3 - Patient Evidence; 2002]. Similarly, NICE allude to patient surveys when identifying themes emerging from stakeholder comment - themes which contributed to the decision that fresh guidance is required: "*Evidence was cited of harms of GET; patient surveys*

appear to contradict findings from randomised controlled trials and systematic reviews regarding the safety and efficacy of CBT, GET and pacing."

3. Biomedical evidence contra-indicating exercise, including abnormal response to exercise

None of the evidence assessed relates to the pathophysiological abnormalities found in patients, including findings demonstrating an abnormal response to exercise.

The absence of this type of information is notable, as themes identified from stakeholder comment at the surveillance review stage - which contributed to the decision by NICE that CG53 requires to be fully updated - included:

1. *"Aetiology is outside the current scope. However many stakeholders raised the issue in respect to its impact on diagnosis and treatment."*
2. *"Biological models based on measurable abnormalities may need greater consideration."*

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The screening out of this evidence enhances the risk that healthcare professionals will not be in a sound position to act in accordance with the law on informed consent:

> *"… The doctor is therefore under a duty to take reasonable care to ensure that the patient is aware of any material risks involved in any recommended treatment, and of any reasonable alternative or variant treatments. The test of materiality is whether, in the circumstances of the particular case, a reasonable person in the patient's position would be likely to attach significance to the risk, or the doctor is or should reasonably be aware that the particular patient would be likely to attach significance to it."* [para 87]
>
> SOURCE: https://www.supremecourt.uk/cases/docs/uksc-2013-0136-judgment.pdf

The issue of informed consent and the requirement to take into account up to date evidence in this regard was identified by NICE as pertinent at the surveillance review stage: "*Stakeholders noted that NICE's evidence reviews are not up to date, therefore patients are not receiving the full picture on recommended treatments (such as studies that have shown inefficacy of cognitive behavioural therapy [CBT] or harms of graded exercise therapy [GET]), nor being told about alternative treatments, which may affect informed consent."*

In addition to the screening out of evidence, as described above, we are concerned that the following paper has been excluded from consideration (this would appear to be the only paper referenced in the evidence reviews which addresses the issue of informed consent):

> Geraghty KJ, Blease C. Cognitive behavioural therapy in the treatment of chronic fatigue syndrome: A narrative review on efficacy and informed consent. Journal of Health Psychology. 2018; 23(1):127-138 [Ref. 281, Evidence Review H]

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LINKS TO DOCUMENTS

Statement on the Guideline Committee and its work, November 2018:

https://www.nice.org.uk/guidance/gid-ng10091/documents/committee-member-list

Scope - stakeholder consultation comments and responses

https://www.nice.org.uk/guidance/gid-ng10091/documents/consultation-comments-and-responses-2

Call for evidence https://www.nice.org.uk/guidance/gid-ng10091/documents/html-content

Surveillance review outcome report

https://www.nice.org.uk/guidance/cg53/resources/surveillance-report-2017-chronic-fatigue-syndromemyalgic-encephalomyelitis-or-encephalopathy-diagnosis-and-management-2007-nice-guideline-cg53-pdf-5964455783941

Surveillance Review: evidence submitted by stakeholders meeting criteria for inclusion

https://www.nice.org.uk/guidance/cg53/evidence/appendix-b-summary-of-evidence-highlighted-to-nice-during-consultation-pdf-4602203535

Wilshire *et al.* 2017 https://www.tandfonline.com/doi/full/10.1080/21641846.2017.1259724

Wilshire *et al.* 2018 https://bmcpsychology.biomedcentral.com/articles/10.1186/s40359-018-0218-3

Forward-ME Survey 2019

Oxford Clinical Allied Technology and Trials Services Unit. Forward-ME Group CBT and GET Survey. 2019 http://www.forward-me.co.uk/assets/images/site-wide/survey-report-27th-march-2019.pdf

Evidence Review G: https://www.nice.org.uk/guidance/gid-ng10091/documents/evidence-review-7

Ref. 65; Table 69: Summary of studies included in the review (identified through the call for evidence), listed as 'Forward-ME Survey 2019' - table confirms that responses to open-ended questions were analysed; none of the findings from these questions feature in the qualitative evidence syntheses (Tables 70-82).

Evidence Review H: https://www.nice.org.uk/guidance/gid-ng10091/documents/evidence-review-8

Ref. 559 - qualitative material emerging is summarised at *2. Experience of interventions; Appendix D - Qualitative evidence tables* (listed as 'Forward-ME Survey 2019, pages 553-555).

OTHER REFERENCES

CMO's Working Group Report 2002

Department of Health (2002): *Report of the CFS/ME working Group*: *Report to the Chief Medical Officer of an Independent Working Group*

Abnormal response to exercise

For example:

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Clinical Case Definition and Guidelines for Medical Practitioners: An Overview of the Canadian Consensus Document Bruce M Carruthers and Marjorie I van de Sande 2005; the table on page 4 of this document summarises the response to exercise in ME/CFS patients as compared to healthy controls, referencing eight original published papers.

The above material is updated in:

Myalgic Encephalomyelitis – Adult & Paediatric - International Consensus Primer for Medical Practitioners International Consensus Panel; co-eds Bruce M Carruthers & Marjorie I van de Sande; 2012; see table on pages 3-4, referenced to 31 published papers.