

*Made on Behalf of the Claimant
Witness: Malcolm Kendrick
1st Statement
Exhibits: MK1 – MK2
Dated: March 2008*

IN THE HIGH COURT OF JUSTICE

CO/10435/2007

QUEENS BENCH DIVISION

ADMINISTRATIVE COURT

BETWEEN:

R (on the application of)

BENJAMIN BRYANT

(by his mother and litigation friend, Jane Bryant)

Claimant

- and -

**THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL
EXCELLENCE (NICE)**

Defendant

WITNESS STATEMENT OF DR MALCOLM KENDRICK

I, Dr Malcolm Kendrick, MbChB MRCP, of 24 Prestwick Close, Tytherington, Macclesfield, Cheshire, SK10 2TH will say as follows:

1. I make this statement in support of the Claimant's application for judicial review of *NICE Clinical Guideline 53 – Chronic Fatigue Syndrome / Myalgic Encephalomyelitis*. Unless I state otherwise, the contents of this statement are within my knowledge. The remainder of the statement is true to the best of my knowledge and belief.
2. I am a General Practitioner and member of the General Practitioners Committee (GPC) of the British Medical Association. I was an original

member of the Centre for Evidence Based Medicine and set up the NICE website. I worked with the European Commission to develop a pan-European system from Continuing Medical Education and then set up the educational websites for the European Society of Cardiology (ESC) and Federation of European Cancer Societies (FECS). I am a peer-reviewer for the British Medical Journal. I worked on the NICE evaluation on Multiple Sclerosis and published a paper on this in *Pharmacoeconomics*¹. I have written widely on cardiovascular medicine, including articles in the *BMJ*².

3. From a general point of view I find the decision of NICE to recommend Cognitive Behaviour Therapy (CBT) and Graded Exercise Therapy (GET) is difficult to understand. The review relied on very few studies, most of which were of poor quality. Many of the studies had different entry criteria and outcome measurements, so could not be compared in any meaningful way.
4. Most of the studies did not use World Health Organisation International Disease Classification criteria (WHO ICD), for reasons that are not explained in the document, and despite the fact that I understand that the Department of Health has accepted this classification.³
5. In fact, in broad terms I would have to agree with the latest conclusions of the York Centre for Reviews and Dissemination who carried out the evaluation of ME/CFS on behalf of NICE⁴. This review was published in February 2007 and updates the October 2005 review which was relied upon by the Guideline Development Group. I refer to it as "Report 35". The Report is attached as **exhibit "MK1"**. The Conclusions of that review can be found at page 41 of their document, and are included below.

¹ *Kendrick M, Johnson KI: Long-term treatment of multiple sclerosis with interferon-beta may be cost effective. 1: Pharmacoeconomics. 2000 Jul;18(1):45-53*

² *Kendrick M: 'Should women be offered cholesterol lowering drugs to prevent cardiovascular disease? NO.' BMJ 2007;334:983 (12 May)*

³ See for instance the evidence submitted by ScottME to the Parliamentary Select Committee on Health, at <http://www.publications.parliament.uk/pa/cm200607/cmselect/cmhealth/503/503we70.htm>

⁴ <http://www.york.ac.uk/inst/crd/pdf/crdreport35.pdf>

Conclusions of York Centre for Review and Dissemination

(On current data available for ME/CFS treatment)

6. A total of 70 trials investigated the effectiveness of seven different categories of intervention: behavioural, immunological, antiviral, pharmacological, supplements, complementary/ alternative and other.
7. Overall the interventions demonstrated mixed results in terms of effectiveness. Conclusions about effectiveness should be considered together with the methodological inadequacies in some of the studies.
8. Interventions which have shown evidence of effectiveness include CBT and GET.
9. There is insufficient evidence about how sub-groups of patients may respond differently to treatments and further studies investigating additional subgroups are needed.
10. In some of the included studies bed or wheelchair restricted patients and children have been excluded, which raises questions about the applicability of findings to all people with CFS/ME.
11. CBT and immunoglobulin G are the only interventions which have been investigated in young people.
12. There is insufficient evidence for additive or combined effects of interventions where more than one therapy is used.

13. Future research could usefully compare CBT and GET and there is a need to evaluate the effectiveness of pacing, ideally in comparison to CBT and GET.
14. Future research needs to combine scientific rigor with patient acceptability.
15. The large number of outcome measures used makes standardisation of outcomes a priority for future research.
16. To paraphrase, there is some (limited) evidence to support the use of CBT and GET in ME/CFS, however – to use the words of the York Review Group itself – *‘future research needs to combine scientific rigor with patient acceptability.’* Up to now there has been little scientific rigour. Studies have used different inclusion data and different outcomes data which makes meta-analysis impossible. In addition, whilst the trials claim to be randomised, they have not been.
17. Possibly the key point in this document is the acknowledgment that *‘standardisation of outcomes (are) a priority for future research.’* With no standardisation of outcomes, you cannot draw conclusions from a meta-analysis, as you are not comparing like with like. This would be like comparing trials on an anti-hypertensive medication where one trial looked at headaches, another looked at strokes, a further one analysed heart attacks, whilst another measured quality of life.
18. The tables on pages 5-7 of Report 35 show that, on psychological measurements, the study outcomes included outcomes as diverse as: depression, anxiety, psychological well being, emotional distress and perceived ability. These different outcomes cannot be effectively compared.
19. With regard to randomisation, I have chosen (due to time constraints), to look at only one study (a study, incidentally, upon which most of the NICE

evaluation hinges). This was the study by Prins et al⁵ (at times referred to as the Severens study). This was considered to be a study of high validity, and was by far the largest of the studies on CBT.

20. However, of 476 patients evaluated initially, only 278 were ‘willing and/or able’ to take part. Whilst this study refers to itself as a randomised controlled trial, nearly 200 people did not wish to take part (and did not take part), prior to ‘randomisation’.

21. Therefore we have a fundamentally biased group to start with i.e. those who are both willing and able to take part, and who may be far more likely to be motivated to report positive results from the intervention. So the trial was not randomised – or ‘random’ – in that it included a self-selected population who were well enough, and motivated enough, to take part. The two hundred who did not take part may have had a completely different result if exposed to CBT. Indeed they should be included in an ‘intention to treat’ analysis at the end of the trial which would significantly alter the results.

22. Another problem with the research used by the Guideline Development Group in the evaluation is the fact that there were very high drop-out rates, around 20-40%, in treatment groups (this information can be seen on page 39 of Report 35 under the heading ‘withdrawals and drop out’). Reasons for the drop-outs were generally unreported, and no adverse effects were reported. If patients dropped out due to adverse events caused by treatment, and these adverse events were not recorded then researchers have, in effect, failed to record any possible harm done by treatment, thus greatly over-estimating benefits.

⁵ Prins JB, Bleijenberg G, Bazelmans E, Elving LD, de Boo TM, Severens JL, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *Lancet* 2001;357:841-7

23. Moreover, individuals may drop out because, even though they are not harmed by a treatment, they derive no benefit from it. Unless that is included in the overall analysis, the results will be distorted and in particular will over-state the benefits of the treatment.
24. A further, major flaw is the fact that ME/CFS is a long-term condition, but most of these trials were of short duration with no follow up. On a reading of the one study that did do follow up after five years it can be seen that the researchers found no differences between the normal protocol and CBT groups in physical findings, fatigue, general health symptoms, relapses or the proportion of participants that no longer met the UK criteria for CFS⁶. In short, the benefits had significantly attenuated after five years.
25. In short, there are very few studies showing benefit from CBT and/or GET. There are others that show no benefit at all. The ‘beneficial’ studies themselves are generally very small. They all have major methodological flaws, they all use different inclusion criteria and/or outcomes measurement.
26. There is, I believe, currently enough evidence to suggest that further studies should be done in this area. However, based on the current data it seems irrational for anyone to recommend CBT and/or GET as clinically effective based on the evidence base presented to NICE.

Cost-Effectiveness

27. Whilst it is clearly important to establish if a therapy is clinically effective (which in the case of CBT/GET is not clear), it is furthermore important to work out if the clinical benefit gained is worth the added cost to the NHS (cost-effectiveness). Cost-effectiveness is a critical component of a NICE

⁶ Deale A, Husain K, Chalder T, Wessely S. Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. *Am J Psychiatry* 2001;158:2038-42

evaluation and failure to meet the criteria for cost-effectiveness forms the basis for NICE refusing healthcare interventions of known clinical benefit e.g. drug treatments for Alzheimer's, flu, and Multiple Sclerosis (to name but three).

28. Professor Sir Michael Rawlins, Chairman of NICE since 1999, wrote in the British Medical Journal in 2004:⁷:

“on its own, clinical effectiveness is insufficient for maintaining or introducing any clinical procedure or process. Cost must also be taken into account.”

I attach this article as **exhibit “MK 2”**.

29. Establishing cost-effectiveness is normally done by working out a health utility model using the Cost per Qaly Adjusted Life Year (cost per QALY figure). A cost per QALY threshold has not been established by NICE, although Professor Rawlins stated in the above article that there needs to be special reason for accepting technologies with ratios over £25-35,000/QALY.

30. The Guideline Development Group sets out the cost-effectiveness evidence statements for CBT/GET at page 197 of the full guideline document (Tab 3, Volume 1, Claimant's Bundle of Documents). The health economics evidence is at pages 200-213. The relevant data extraction tables are at appendix 2 to the full guideline document.

31. It appears from this document that, in the case of GET for treatment of ME/CFS, no attempt has been made to establish any health utility model at all. There has been no attempt to establish a cost per QALY, nor to make any

⁷ Rawlins M. Culyer A. National Institute for Clinical Excellence and its value judgments. BMJ 2004;329:224-227 (24th July)

other attempt to define the cost-effectiveness of this intervention. Only one study looked at cost per QALY for GET compared to CBT, and it was unable to show any difference in cost-effectiveness⁸. There are no studies of GET vs. either standard care or no care.

32. In the case of CBT, there are only two studies that have looked at cost effectiveness. One showed no benefit from CBT⁹, so the cost per QALY was infinite. The other did show some benefit from CBT. This was the Severnes/Prins study. From this single study NICE assessed the cost per QALY at £16,603 (page 207 of guidelines).
33. This is within the NICE threshold for accepting interventions. However, it must be remembered that this used data from one study only (the Prins.Severens study), and on further evaluation of this study the data must be considered extremely unreliable for the reasons which follow.
34. Firstly, as the guidelines themselves state (Page 201 of guidelines), there was a difference in the measured quality of life between the CBT group and the control group at the start of the study. The figures were: quality of life: 0.486 for the CBT group, and 0.526 for the control group. In short the two groups were not comparable at the start of the study, with the control group having a higher quality of life than the group allocated to CBT. The quality of life in the control group was 0.04 higher – this may seem insignificant, but it becomes critical for any meaningful analysis.
35. The reason why this figure of 0.04 is highly significant is that the difference is quality of life at the start of the study was 0.04. At the end of the study the

⁸ *McCrone P, Ridsdale L, Darbishire L, Seed P, Cost-effectiveness of cognitive behavioural therapy, graded exercise and usual care for patients with chronic fatigue in primary care. Psychological Medicine 2004;34:991-999*

⁹ *Chisholm D, Godfrey E, Ridsdale L, Chalder T, King M, Seed P, Wallace P, Wessely S and the Fatigue Trialists' Group. Chronic fatigue in general practice: economic evaluation of counselling versus cognitive behaviour therapy. BJGP 2001;51:15-18*

difference between the two groups was 0.0015. So, the quality of life difference was 26.6 times higher at the start than the end of this trial. So, whilst the figure of 0.04 may appear – on the face of it – insignificant, it is 26.6 times greater than the measured difference at the end. So, clearly, it introduces massive (and uncorrected) bias into the analysis of this trial.

36. This means that the control group had a higher measured quality of life at the start of study, than the CBT group. And, to quote from the guidelines themselves (page 201 of guidelines) *‘there does not appear to have been any attempt to correct for this difference between the comparison groups, and this may have led to bias in the analysis.’*

37. It appears that the Guideline Development Group made no attempt to correct for bias primarily because, as they admit, *‘we did not have access to the trial data. Therefore we resorted to other methods...’* (see page 209 of the guidelines, first paragraph). Although they do say that, as they could not correct for a potential bias, they reduced the reported utility gain, they also say that their sensitivity analysis shows that if baseline differences are corrected, there could be a significant impact on the result. It would be more accurate to say that, if baseline differences were corrected, there *would* have been a significant impact on the results. This all begs the question as to why no one did this.

38. One would have to say that, in reality, this baseline difference represents a major problem that makes any rational analysis impossible. If there are two groups which are supposedly randomised, yet one group is significantly different to the other at baseline, this is a biased sample and, realistically, makes further analysis invalid.

39. An additional problem is that as the control group started with a higher quality of life, it was always going to be more difficult for them to improve to the

same degree as those in the CBT group who started with a lower quality of life. This is reflected by the fact that, at the end of the trial – although the CBT group improved their quality of life to a greater extent than the control group – at the end of the study the total difference in quality of life between the two groups was 0.0015¹⁰ of a QALY (a figure so small as to be completely statistically insignificant, and for a patient absolutely clinically insignificant).

40. The NICE appraisal group fully accepts this figure (page 209 of the guidelines, final figure on Table 7). Although they have taken it to more decimal places, at 0.001579.

41. In reality, this figure represents the true difference in quality of life between the two groups at 14 months, and is therefore the only figure that can be used without bias. Using this figure, the cost per QALY for CBT is £283,420.81.

42. Perhaps most telling, and almost unbelievable, is that the Guideline Development Group, when calculating the cost per QALY, used the wrong figures. This is such a fundamental error that it must throw everything else in this document into huge doubt.

43. In Table 2 (page 201 of the guidelines) the improvement in the CBT group was from 0.4859 to 0.6014. This is a difference of 0.1155 – not 0.0737 as reported in table 4, page 207. The improvement in the control group was from 0.5257 to 0.5999, a difference of 0.0742. However, NICE have stated that the reported improvement in the control group was 0.0458, so this figure is also wrong.

¹⁰ In the CBT group the quality of life was 0.4859 at the start of the study, 0.5817 at 8 months and 0.6014 at 14 months. In the control group the quality of life was 0.5257 at the start of the study 0.5779 at 8 months, and 0.5999 at 14 months. (A difference of 0.0015 between the CBT and control group at 14 months)

44. Not unsurprisingly, the figure they established as the difference between the two groups is, therefore, completely wrong as well. I find it incomprehensible that a report of such significance can contain such major, and simple, errors.

Summary of cost-effectiveness analysis

GET

45. There has been no attempt made to analyse cost effectiveness for this intervention.

CBT

46. The analysis relies, entirely, on a single positive study.
47. The study was flawed due to major bias at baseline between the two groups. This bias was uncontrolled for by the study authors, and by NICE who admit that they did not have access to the trial data (see page 209, first paragraph).
48. At the end of the study the difference between the CBT and control groups was 0.0015 of a QALY, which is statistically and clinical insignificant. This difference also equates to a cost per QALY of £283,420.81 (This is the NICE figure on page 209 of the guidelines).
49. The analysis of the cost per QALY data contains simple, but major, arithmetical errors.
50. I would recommend that a group of 'experts' not tied to the psychological/psychiatric model of ME/CFS should be asked to analyse the NICE review. Currently it is very weak from a clinical standpoint, (and provides an insufficient basis to make the clinical evaluations that have been made), and non-existent from the key NICE criteria of cost-effectiveness.

STATEMENT OF TRUTH

I believe that the facts stated in this witness statement are true.

Dated this 27th day of March 2008

Signed....Malcolm E.S. Kendrick.....

MALCOLM KENDRICK

*Made on Behalf of the Claimant
Witness: Malcolm Kendrick
1st Statement
Exhibits: MK1 – MK2
Dated: March 2008*

IN THE HIGH COURT OF JUSTICE

CO/10435/2007

QUEENS BENCH DIVISION

ADMINISTRATIVE COURT

BETWEEN:

R (on the application of)

BENJAMIN BRYANT

(by his mother and litigation friend, Jane Bryant)

Claimant

- and -

**THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL
EXCELLENCE (NICE)**

Defendant

EXHIBIT “MK 1”

This is the exhibit marked “MK1” referred to in the first witness statement of Malcolm Kendrick dated March 2008.

Signed... *Malcolm Kendrick*

Malcolm Kendrick

Dated *27/3/08*

Made on Behalf of the Claimant
Witness: MK
1st Statement
Exhibits: MK1 – MK2
Dated: March 2008

IN THE HIGH COURT OF JUSTICE

CO/10435/2007

QUEENS BENCH DIVISION

ADMINISTRATIVE COURT

BETWEEN:

R (on the application of)

BENJAMIN BRYANT

(by his mother and litigation friend, Jane Bryant)

Claimant

- and -

**THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL
EXCELLENCE (NICE)**

Defendant

EXHIBIT “MK 2”

This is the exhibit marked “MK2” referred to in the first witness statement of Malcolm Kendrick dated March 2008.

Signed... *Malcolm Kendrick*

Malcolm Kendrick

Dated 27/7/08