TECHNOLOGY ASSESSMENT REPORTS FOR THE HTA PROGRAMME

A review of the clinical and cost effectiveness of cannabinoids (cannabis derivatives) for treatment of the symptoms of multiple sclerosis (HTA 02/23)

A. **Draft version. Note: this protocol is provisional and subject to change.**

B. **Details of review team**

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C. **Full title of research question: A review of the clinical and cost effectiveness of cannabinoids (cannabis derivatives) for management of the symptoms of multiple sclerosis (HTA 02/23)**

D. **Clarification of research question and scope**

The overall aim of this review will be to consider the evidence concerning the clinical and cost effectiveness of cannabis based medicine extract (CBME, GW Pharmaceuticals) and dronabinol (Marinol®, Solvay Healthcare Ltd.) within their anticipated licensed indications, compared to standard current pharmacological treatment for the relief of symptoms associated with multiple sclerosis. Where evidence allows, this review will include reductions in MS-related spasticity and muscle spasm, pain (chronic refractory pain, neuropathic pain and other types of pain), tremor, bladder dysfunction and lower urinary tract problems, sleep disturbance, as well as psychological effects such as depression. The assessment of CBME and dronabinol in the management of further

MS symptoms will be determined by the existence of evidence. The review will include any significant impacts of CBME and dronabinol on health-related quality of life.

This assessment will take into account any dose-related effects arising from management with dronabinol or CBME. If evidence allows, the review will attempt to identify criteria for selecting patients for whom treatment with CBME or dronabinol would be particularly appropriate.

More specifically, the review of CBME and dronabinol in the management of MS-related symptoms aims to:

(1) evaluate the clinical effectiveness of CBME and dronabinol within their anticipated licensed indications*
(2) estimate the impact of CBME and dronabinol on health-related quality of life*
(3) evaluate the adverse effect profile and toxicity for CBME and dronabinol
(4) estimate the incremental cost effectiveness of the interventions in comparison to standard current pharmacological treatment*
(5) estimate the overall cost to the NHS in England and Wales of routinely offering CBME and dronabinol for the management of symptoms associated with MS*

* *The synthesis of evidence concerning both the clinical and cost effectiveness of CBME and dronabinol is dependent on the evidence available at the time of the assessment.*

E. **Report Methods**

Search strategy

The search strategy will aim to identify all studies relating to CBME and dronabinol in the management of symptoms associated with multiple sclerosis. Search strategies will include the terms tetrahydrocannabinol (THC), cannabidiol (CBD), cannabinoid, cannabis based medicine extract (CBME), cannabis, dronabinol, and multiple sclerosis. The following databases will be searched: Medline (1966-Present), Embase (1980-Present), the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Controlled Trials Register (CCTR), and the NHS Centre for Reviews and Dissemination databases (DARE, NHS EED, HTA). Pre-Medline will also be searched to identify any studies not yet indexed on Medline. Current research will be identified through searching The National Research Register (NRR) the Community of Science (COS) Funded Research database, the Current Controlled Trials register and the MRC Clinical Trials Register. Any industry submissions, as well as any relevant systematic reviews will also be hand-searched in order to identify any further clinical trials. Searches will not be restricted by language, date or publication type.

Inclusion criteria

Population: Individuals with multiple sclerosis. More specifically, this will include those patients who are eligible for treatment with dronabinol or CBME according to their anticipated licensed indications.

Intervention: CBME or dronabinol

Comparators: Current pharmacological treatment to relieve the symptoms associated with MS.

Outcomes will include:

- Spasticity and spasm
- Neuropathic, chronic refractory and other types of pain
- Tremor
- Bladder dysfunction/ micturition problems

- Sleep disturbance
- Incidence of adverse events, psychological effects
- Health-related quality of life.

Research Design:
Systematic reviews
Randomised controlled trials
Non-randomised controlled trials (in the absence of RCT evidence)
Economic evaluations

Exclusion criteria

Reviews of primary studies will not be included in the analysis, but will be retained for discussion. Studies enrolling mixed patient populations will only be included if the results of the MS sub-groups are reported separately.

Data extraction strategy

Customised data extraction forms will be developed to incorporate critical appraisal checklists and the Jadad quality scale.[1] Data will be extracted by one researcher, and checked by a second. Any disagreements arising from this process will be resolved by discussion.

Quality assessment strategy

Studies will be evaluated according to the accepted hierarchy of evidence, whereby meta-analyses of randomised controlled trials are taken to be the most authoritative forms of evidence, and uncontrolled observational studies the least authoritative.[2] The quality of systematic reviews and meta-analyses will be assessed using the guidelines from the Centre for Health Evidence based upon the Users Guides to Evidence-based Medicine.[3] Where appropriate, the quality of randomised controlled trials will be assessed using the Jadad scale[1] which addresses randomisation, blinding and the handling of study withdrawals and dropouts.

Use of data from non-randomised studies will be considered if there is insufficient evidence available from good-quality randomised controlled trials. The quality of non-randomised trials will be assessed using the guidelines from the Centre for Health Evidence based upon the Users Guides to Evidence-Based Medicine.[4]

It is anticipated that evidence of the economics of CBME and dronabinol in the management of symptoms associated with multiple sclerosis will be limited, however the search strategy will be developed to ensure that all existing evidence is identified and systematically reviewed. The quality of economic literature will be assessed according to current good practice guidelines.[5;6]

Methods of analysis/synthesis

The methods of analysis and synthesis of evidence will be determined by the availability, volume and homogeneity of studies reported in the literature.

Methods for estimating qualify of life, costs and cost effectiveness and/or cost/QALY

If appropriate, a mathematical model will be constructed to synthesise the available evidence on the reduction in the symptoms of MS and the resulting impact upon health-related quality of life deriving from CBME or dronabinol.

Where possible, costs will be obtained from published studies of MS, although it is likely that such evidence will be scarce. Cost data will be incorporated into the mathematical model in order to assess both the cost and clinical effectiveness of CBME and dronabinol.

If evidence allows, the primary outcome will be the cost per quality adjusted life year gained will be estimated.

F. **Handling the company submission(s)**

Hand searching of the company submissions will be performed in order to identify whether cost effectiveness and cost utility analyses have been published. If such economic studies are identified, these will be reviewed systematically.

If appropriate, an independent economic model will be developed in order to estimate the costs and health gains resulting from dronabinol and CBME. If such evidence is available, this model will estimate the cost utility associated with dronabinol and CBME. As dronabinol and CBME do not impact upon patient survival, a life years gained approach will not be appropriate.

Owing to the expected paucity of evidence on the effects of dronabinol and CBME, it is envisaged that the company submissions will be used primarily as a key source of data on treatment effects, costs, and health gains; the availability of data from the MRC CAMS trial and the GW trials will be pivotal to the development of an independent economic model (and indeed the review of clinical effectiveness). Secondly, the ScHARR model will be used to assess economic analyses submitted by the companies. If possible, the ScHARR economic model will be developed in advance of the industry submissions using evidence available in the public domain and expert clinical advice. If appropriate, the ScHARR model will then be compared against the economic analyses reported within the industry submissions, taking into account the respective strengths and weaknesses of each.

G. **Project Management**

a. **Timetable/milestones**

Milestone	**Date expected**
Draft protocol	26th February 2003
Finalised protocol	19th March 2003
Progress report	18th June 2003
Final draft report to external reviewers	28th July 2003
Assessment report	28th August 2003

b. **Competing Interests**

None

c. **External reviewers**:

The Technology Assessment Report will be subject to external peer review by at least two experts. These reviewers will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that methodological review will be undertaken by the NICE secretariat and Appraisal Committee, but if the TAR encounters particularly challenging methodological issues we will organise independent methodological reviews. External expert reviewers will see a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. All reviewers are required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking. We will send external reviewers' signed copies to NCCHTA. Comments from external reviewers and the Technical lead, together with our responses to these will be made available to NCCHTA in strict confidence for editorial review and

approval.

H. Appendices

References

1. Jadad AR. Moore RA. Carroll D. Jenkinson C. Reynolds DJ. Gavaghan DJ. Et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials*. 17(1):1-12, 1996.

2. Centre for Reviews and Dissemination, Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD report number 4, March 2001, York: CRD.

3. Oxman AD, Cook DJ, Guyatt GH. Users' guides to the medical literature. JAMA 1994; 272 (17): 1367-1371.

4. Levine M, Walter S, Lee H, Haines T, Holbrook A & Moyer V. Users' guides to the medical literature. JAMA 1994 May 25; 271 (20) 1615-1619.

5. Drummond M F, Jefferson T O, Guidelines for authors and peer reviewers of economic submissions to the BMJ, *BMJ* 1996;313: 275-283

6. Eddy DM. Technology assessment: The role of mathematical modelling. *In: Assessing medical technology*, Washington DC: National Academy Press, 1985

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