NICE National Institute for Health and Care Excellence

Health Technology Assessments of disease-modifying therapies for the treatment of relapsing–remitting multiple sclerosis – challenges in NICE technology appraisals

Background

NICE has encountered various evidential, clinical and methodological challenges during its Health Technology Assessments (HTAs) of disease-modifying therapies (DMTs) for the treatment of relapsing–remitting multiple sclerosis (RRMS).

Risk Sharing Scheme

History

- Uncertainty if treatment benefit of DMTs persisted over long-term → NICE guidance (2002) **did not recommend** betaferons and glatiramer acetate
- NHS and manufacturers agreed to create **risk sharing scheme (RSS) to make these treatments available**
- 2 yearly analyses: if outcomes deviated from target then price of drugs would be adjusted to restore cost-effectiveness
- Data to inform review of guidance

Data from RSS used in economic model[1]

- Over **4000 patients** with RRMS – 10 years of data available for over 3000 patients
- Efficacy data based on summary measure of disease progression through Expanded Disability Status Scale (EDSS) states compared with historical cohort

Table 1: How did the RSS affect NICE committee's modelling preferences?[2]

	Trials	RSS data and committee conclusions
Follow up	Median: 24 months	10 years → **RSS preferred**
Population	Multiple countries	Patients in NHS - 72 centres → **RSS reflects NHS practice**
Efficacy	Meta analysis - DMTs similar	Pooled and individual efficacy estimates for DMTs Committee **preferred pooled** to limit risk of selection bias
Waning of treatment effect	Insufficient follow up to capture	Decrease in effect over time observed → **RRS accounts for waning** for first 10 years
Stopping treatment	Limited long term data	Stopping rates for DMTs were similar → **pooled stopping rate** from RSS used

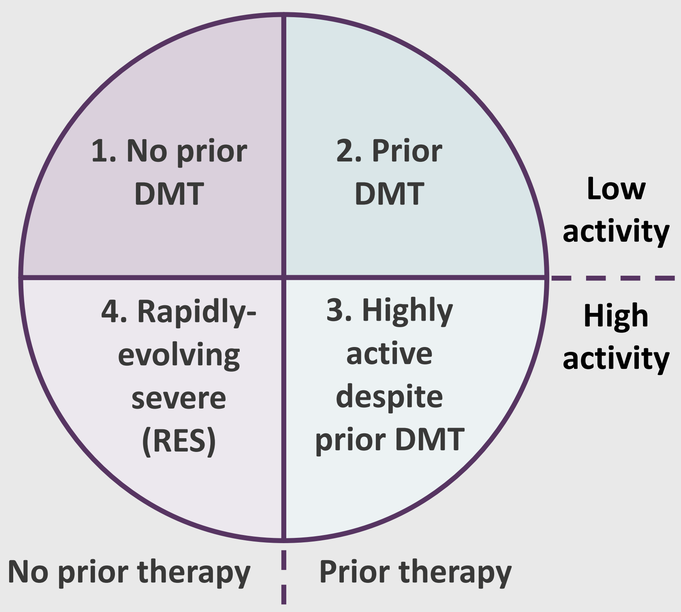
Outcome of TA527 (review of 2002 decision):

Betaferons and glatiramer acetate cost-effective → recommended for use in the NHS – **data from RSS had crucial role** in addressing key uncertainties

Clinical landscape

Treatment landscape continuously changing, with new treatments, subgroups and diagnostic criteria. Challenging to ensure NICE guidance reflects current practice.

Figure 1: RRMS subgroups



Challenge: definitions of subgroups vary across trials → not always clear which recommended treatments are suitable

What are we doing? Developing tool in collaboration with clinicians to **clarify recommended treatment options using clear clinical criteria** including relapses, MRI evidence of activity and treatment history

Case study: cladribine and MRI criteria[3]

RES RRMS: MRI evidence required in current recommendations (TA493)
at least 1 T1 Gadolinium (Gd)-enhancing lesion

↓

We were told:
Historic safety concerns → Gd not always available in hospitals
T2 lesion load can be used to diagnose RES → Gd not always required

↓

Draft recommendations after review of TA493:
at least 1 T1 Gd-enhancing lesion **or a significant increase in T2 lesion load compared with a previous MRI**

Common uncertainties

Table 2: sources of natural history data[4]

Source	London Ontario	British Columbia
Date	1972-1989	1980-1995
Population	Separate analysis of RRMS and SPMS	Includes RRMS and SPMS
Transitions	No improvement in EDSS states	Improvement in EDSS allowed
Subgroups	**No data on key subgroups**: companies have used data from placebo arm of trials or adjusted progression rates	

Mortality rates

- Many appraisals derive mortality ratios from Pokorski (1997)[5] → **may overestimate mortality** as care improved since study
- Data available from Jick (2014)[6] but does not provide **mortality ratios by EDSS state** → implausible rates in some EDSS states

Health state costs

Committee prefers UK MS survey (2005) updated with current unit costs

Strengths
Large data set (n=2048)
Separate NHS and government costs

Limitations
Little data on EDSS >6
Exact composition of costs unclear

Waning of treatment effectiveness

- Long term efficacy of DMTs often uncertain
- Models should include scenario analyses **exploring waning of efficacy** post follow up
- Association between neutralising antibodies and efficacy plausible but **lack of detailed evidence** on strength of any association

Research which could address uncertainties:

- **Natural history data** reflecting advances in standard care and key subgroups
- **Data on costs** from an NHS/PHS perspective, particularly in higher EDSS states
- **Data on mortality** for individual EDSS states
- Investigate association between **neutralising antibodies and treatment efficacy**

References:

1) Palace J et al. *J Neurol, Neurosurg Psychiatry* 2019;**90**:251-260.
2) NICE TA527: https://www.nice.org.uk/guidance/ta527
3) NICE TA493, https://www.nice.org.uk/guidance/ta493
4) Palace J et al. *BMJ Open* 2014;**4**:e004073.
5) Pokorski RJ *J Insur Med* 1997;**29**(2):101-106
6) Jick SS et al. *J Neurol* 2014;**261**(8):1508-1517

For an overview of NICE technology appraisal guidance see MS pathway: https://pathways.nice.org.uk/pathways/multiple-sclerosis

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