INTRODUCTION
Multiple sclerosis (MS) is a chronic immune-mediated disease characterised by inflammation in the central nervous system, causing symptoms such as problems with movement and sensory disturbances, which usually follow a relapsing-remitting pattern (RRMS) before progressing to the secondary-progressive phase (SPMS).

Disease-modifying therapies (DMTs) are immunomodulatory drugs which reduce the number of relapses in patients with MS. The National Institute for Health and Care Excellence (NICE) has completed Health Technology Appraisals for a number of DMTs with marketing authorisations in the European Union.

OBJECTIVES
This systematic review seeks to systematically identify and critically evaluate model structures and assumptions used to date in health economic models of DMTs for RRMS from a UK perspective, and proposes practical recommendations for future modelling to address the underlying drawbacks of models published to date.

METHODS
A systematic review was conducted based on the Cochrane handbook for systematic reviews, where appropriate.

To merit inclusion in the review, publications were required to meet the following criteria: the participants had a diagnosis of RRMS; the intervention was any DMT authorised for use in the UK to treat RRMS; a comparison was made with any other therapy, or no treatment; the outcomes included both costs and clinical outcomes; and the study design was any form of economic evaluation. Publications were excluded if they did not represent full original reports.

RESULTS
The review included a total of 18 reports, relating to 12 different models. The information sources and search strategy used are summarised in Figure 1.

Evolution of Models
There has been increasing standardisation across several key aspects of UK RRMS models over time, in particular since NICE commissioned a new health economic model of RRMS DMTs, known as the SchARR model,17–25 resulting in a convergence upon a more standardised “Post-SchARR” model (Figure 2).

Prior to this, RRMS models were very diverse in terms of model structure and assumptions. These models often did not capture the complexities of multi-faceted RRMS disease progression, subgroup treatments, and effect outcomes, and did not report long-term disease activity and disability.

Features of the Post-SchARR Models
1. Common Features
All post-SchARR models17–25 describe themselves as being based on the SchARR model17–25 and are characterised by several common features that address many of the problems common amongst pre-SchARR models and better reflect real-world RRMS disease progression (Figure 2). In recent years, post-SchARR models have evolved in response to changes in RRMS treatment and care:
- Best supportive care (BSC) has been removed as a comparator from NICE appraisals, as patients now receive BSC alone for MS treatment.
- Treatment sequences of DMTs are now considered to reflect the increasing number of DMTs available.

2. Remaining Diversity of Model Assumptions
- Changes in efficacy and/or discount rate over time are assumed to occur in some models, but not others, and the assumed changes varied between models that incorporated them.
- This could have important implications for future DMT comparisons; for example, applying a percentage decrease in efficacy to all comparators would actually favour less effective therapies when comparing incremental differences.
- Some models20,21,23,25 incorporate all-cause trial withdrawal, whilst others21,23 employ trial withdrawal due to adverse events (AE) alone. Non-intuitively, a higher discontinuation rate can increase cost-effectiveness.22
- Each DMT was modelled with different AE costs and disutilities in different models, with some models21–23 using AEs from external sources or not even clear as to the reason for the inclusion of AEs, whereas others18,20,23 provide a clear algorithm for the inclusion or exclusion of AEs.
- Some patients with MS experience spontaneous improvements in condition,20–22 however, this has only been incorporated within the natural history progressions in some of the more recent post-SchARR models.20,22 Costing improvements in Expanded Disability Status Scale (EDSS) scores could make MS appear more severe than it is.

LIMITATIONS OF POST-SCHARR MODELS

2.1 Sensitivity Analysis
Post-SchARR model features
- Inclusion of AEs
- Discounting of costs
- Clinical assumptions
- Transition matrix

Figure 3. Post-SchARR model features

Common features in response to the SchARR model
- Changes to reflect modern MS treatment
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POST-SCHARR MODEL FEATURES

- In post-SchARR model, all DMTs are considered for the management of RRMS.
- The time has come for a paradigm shift in UK RRMS models to reflect the clinical advances of the last decade.
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