# Natalizumab and its biosimilar for treating highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy: Discrete Event Simulation

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# Outline

- Decision problem
- Previous NICE models in RRMS
- Discrete event simulation and model structure
- MS Registry analyses
- Efficacy, costs and utilities
- Implementation with DESCEM (Warden)
- Results
- Value of information analysis
- Conclusions/learnings

# Decision problem

# NICE Decision problem

- NICE multiple treatment assessment (MTA) .
- Technologies of interest for this appraisal were natalizumab (Tysabri, Biogen) and natalizumab biosimilar (Tyruko, Sandoz).
- Natalizumab is recommended as first-line treatment option for this sub-population of relapsing–remitting multiple sclerosis (RRMS) (NICE TA127).
- The population is highly active relapsing-remitting multiple sclerosis (HARRMS) after at least one disease modifying therapy (i.e., from 2nd line therapy).

# Iinterventions

- Glatiramer acetate
- Interferon beta 1a
- Interferon beta 1b
- Alemtuzumab
- **Cladribine tablets**

Sphingosine 1-phosphate Receptor Modulators

- Ponesimod
- Fingolimod

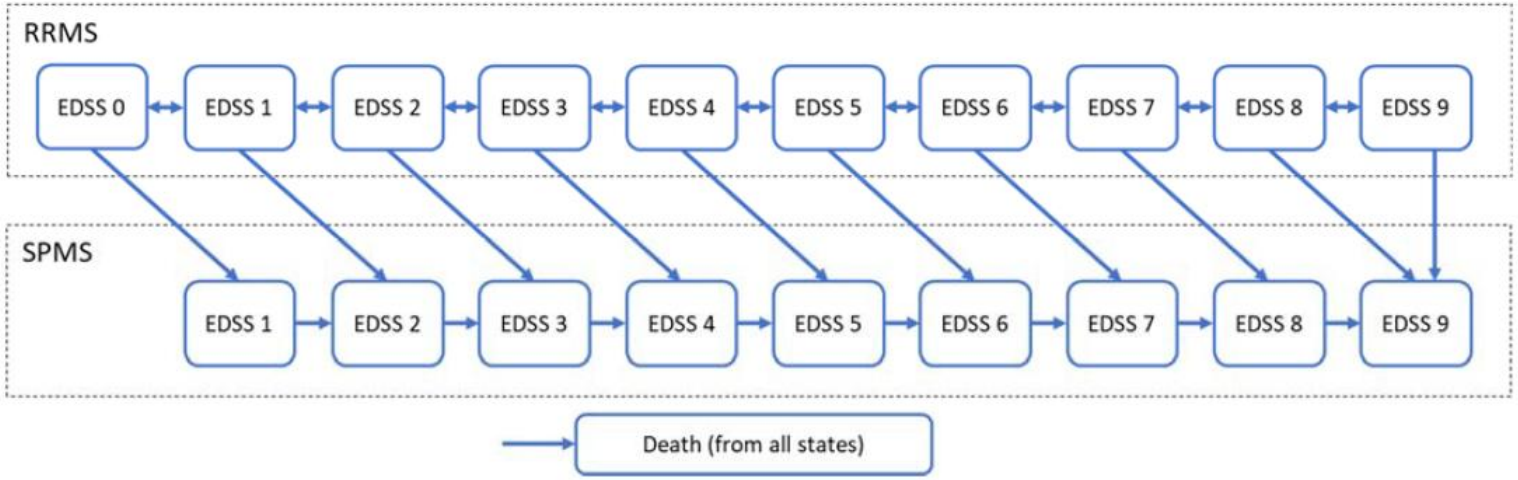
CD-20 Cytolytic Antibodies

- **Ocrelizumab**
- **Ofatumumab**
- **Ublexitumab**

# Previous NICE models in RRMS

# Overview

- 7 STAs (TA767, TA699, TA616, TA533, TA312, TA254 and TA127) , 1 MTA  and 1 cost comparison (TA 1025) for approved drugs in RRMS,
- 21 Health state Markov Model is most common structure




*Source: Ponesimod for treating relapsing multiple sclerosis [ID1393] Document B 29 April 2021. TA767*

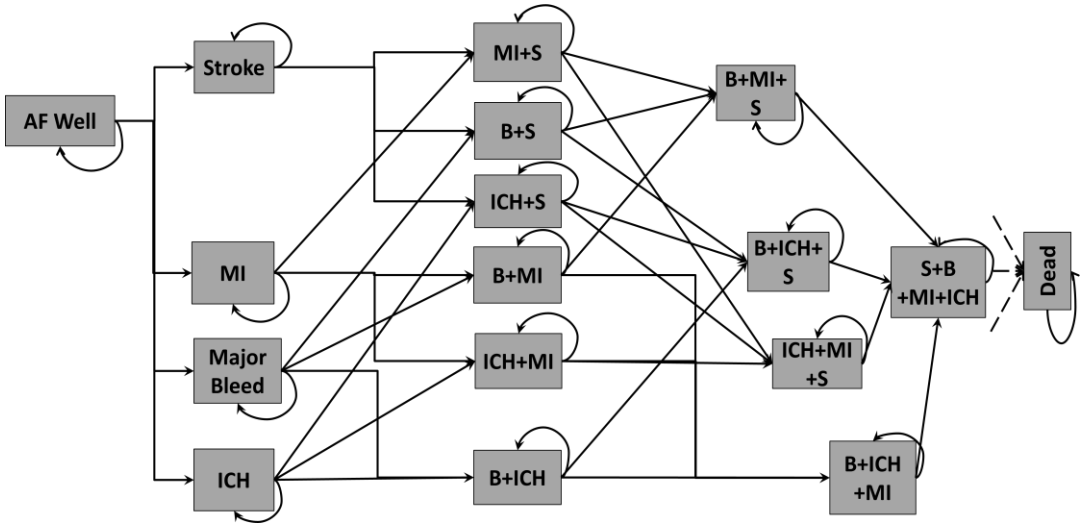
# Key Issues with Previous Models

- Lacking treatment sequencing and variable treatment waning.
- Outdated relative risk of death dependent or independent to severity states.
- Limited ability to accurately reflect the course of the condition and relying on outdated registry data.

# Discrete Event Simulation and model structure

# Events or states for modelling

- Cohort models could be used to record history
- Very quickly proliferate states if need to reflect severities or patient history…illustrated by the Atrial fibrillation model used in NICE clinical guidelines (1)
- Individual level ‘ microsimulation’ is cleaner as patient history can be recorded
- State-based microsimulation of treatment sequences has been employed in Dutch RRMS guidelines (2)
- We argued for events as the treatment effects are primarily on events Confirmed Disability Progression (CDP) and relapses, rather than severity (e.g., EDSS level)




1. NICE. Atrial fibrillation: diagnosis and management. The National Institute for Health and Care Excellence Guideline [NG196]. Available from: https://www.nice.org.uk/guidance/ng196 Site accessed 18/10/22. 2021
2. Versteegh MM, Huygens SA, Wokke BWH, et al. Effectiveness and Cost-Effectiveness of 360 Disease-Modifying Treatment Escalation Sequences in Multiple Sclerosis. *Value Health* 2022;25(6):984-91. doi: 10.1016/j.jval.2021.11.1363

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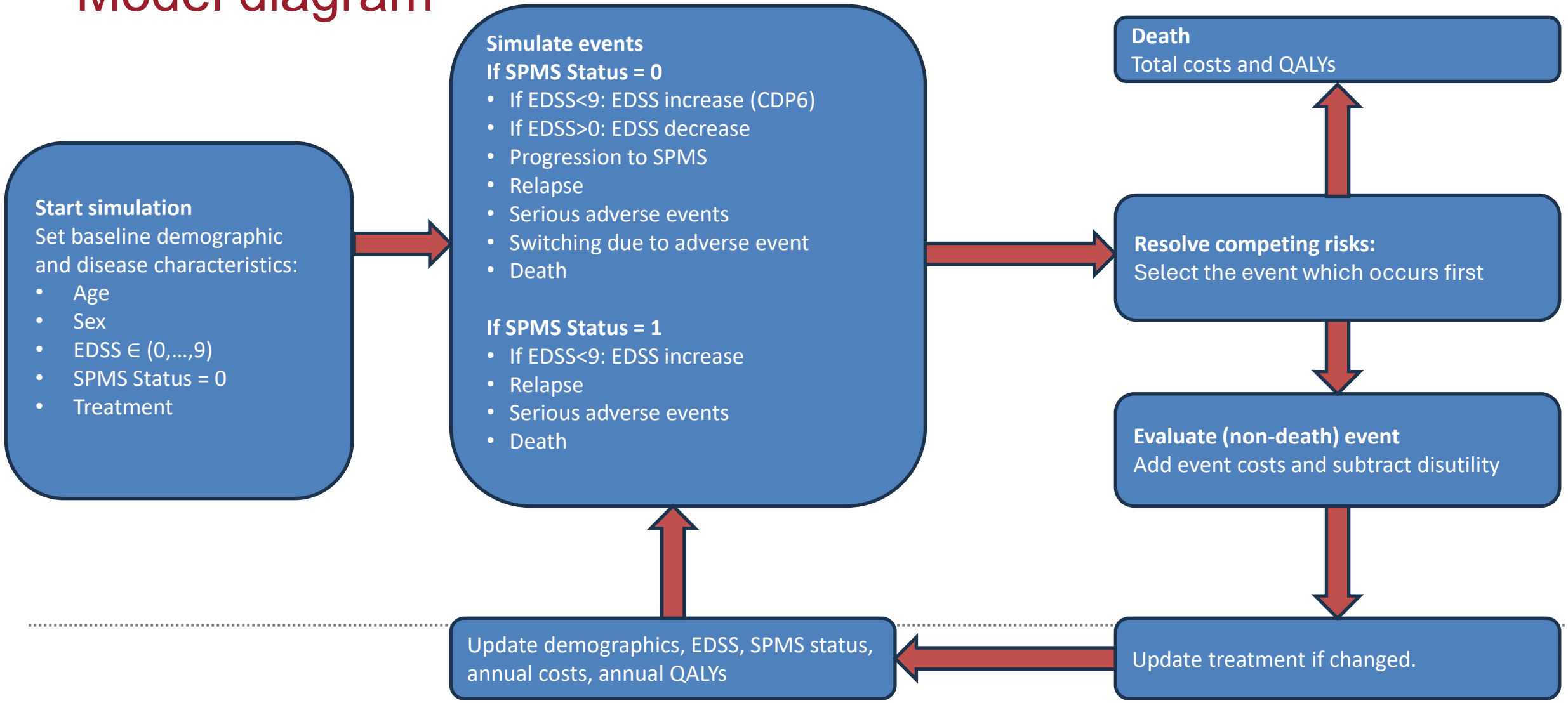
# Model diagram

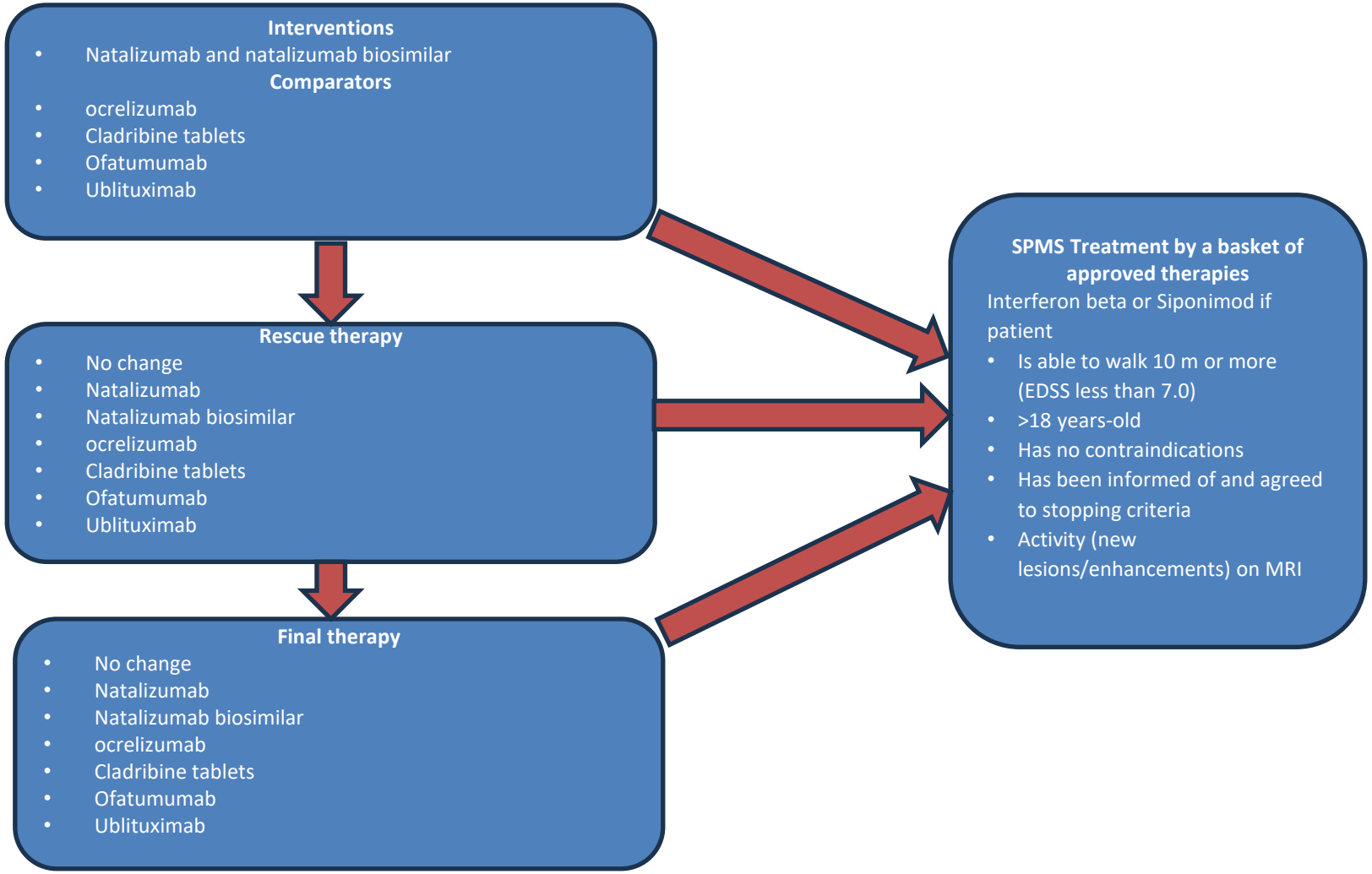


# Treatment sequence

2nd line therapy in highly active RRMS

3rd line therapy in highly active RRMS

4th line therapy in highly active RRMS



# MS Registry Analyses

# Registry Analyses

- Rates of events using exponential survival and models fit to interval censored data. Covariates were included in some of these models.
- Rates depending on treatment used in the model were for patients on Natalizumab-IV

| Event | Covariates |
|---|---|
| **EDSS increase (i.e., confirmed disability progression)** | Treatment, current EDSS |
| **EDSS decrease** | Current EDSS |
| **Relapse** | Treatment, current EDSS |
| **Progression to SPMS** | Current EDSS |

# Mortality

# Updated Mortality

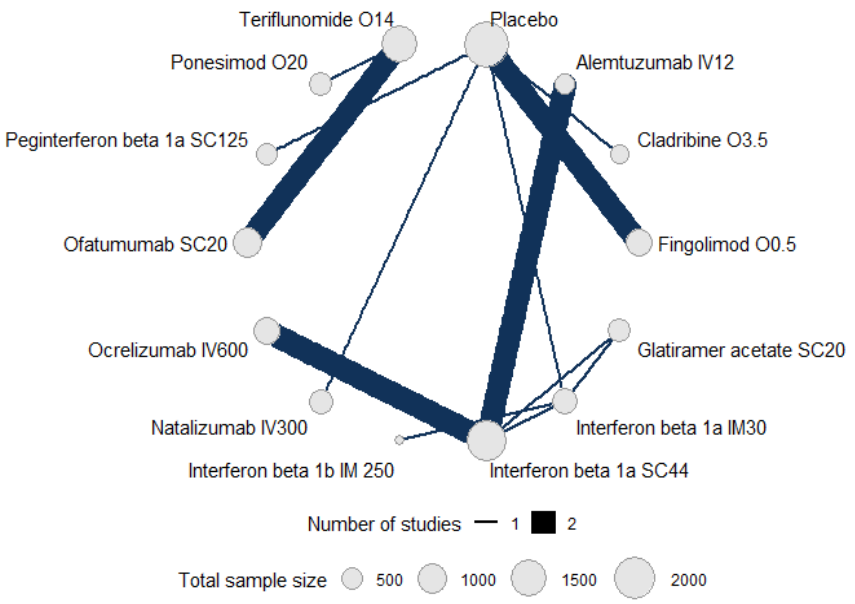
- Updated approach uses average SMR across EDSS levels from Jick 2014 with differences between EDSS categories matched to Harding 2018
- SMRs calculated relative to EDSS 4 based on model simulation that showed highest % time spent in EDSS 4

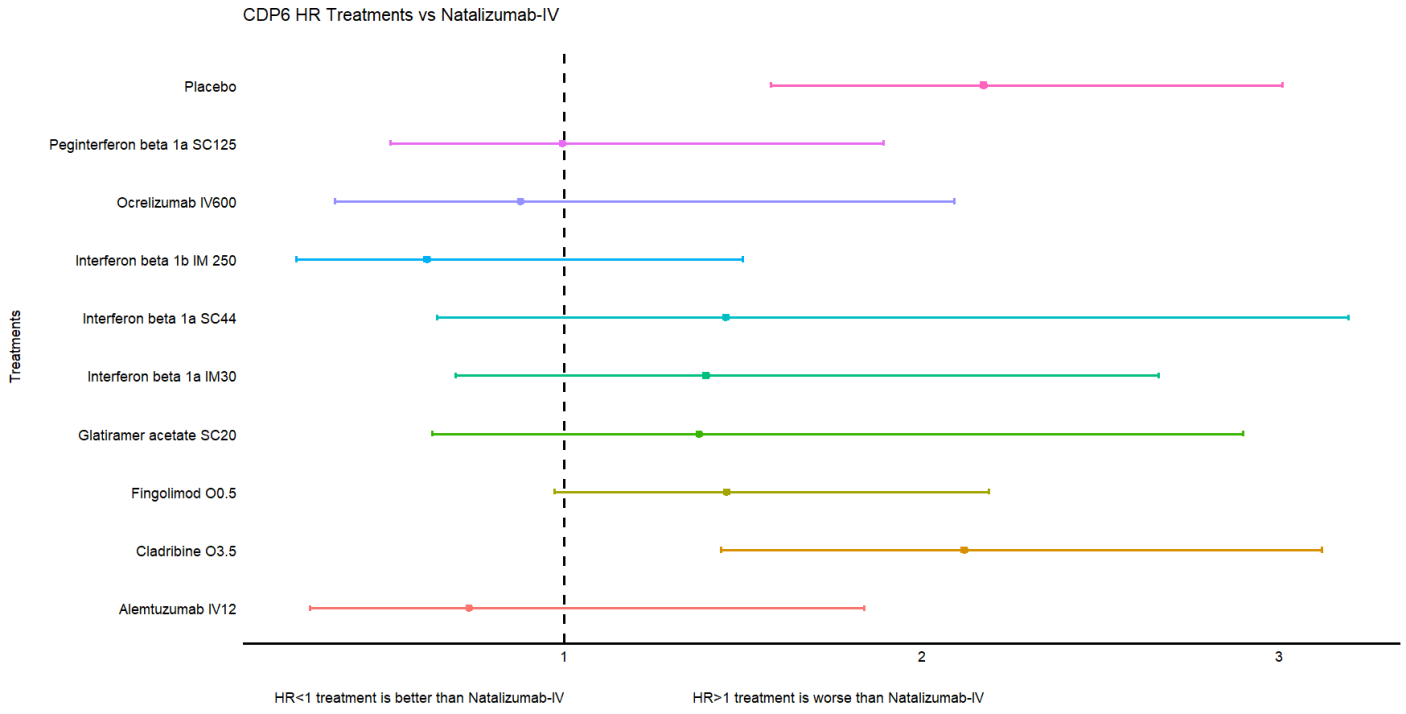
| EDSS | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|---|
| Jick 2014 | 1.68 | 1.68 | 1.68 | 1.68 | 1.68 | 1.68 | 1.68 | 1.68 | 1.68 | 1.68 |
| Harding for EDSS≥4 and Jick for EDSS<4 | 1.68 | 1.68 | 1.68 | 1.68 | 2.02 | 2.02 | 3.86 | 4.76 | 22.17 | 60.74 |
| **Jick/Harding mix SMR** | **1.40** | **1.40** | **1.40** | **1.40** | **1.68** | **1.68** | **3.21** | **3.96** | **18.44*** | **50.52*** |

*SMRs not in base case

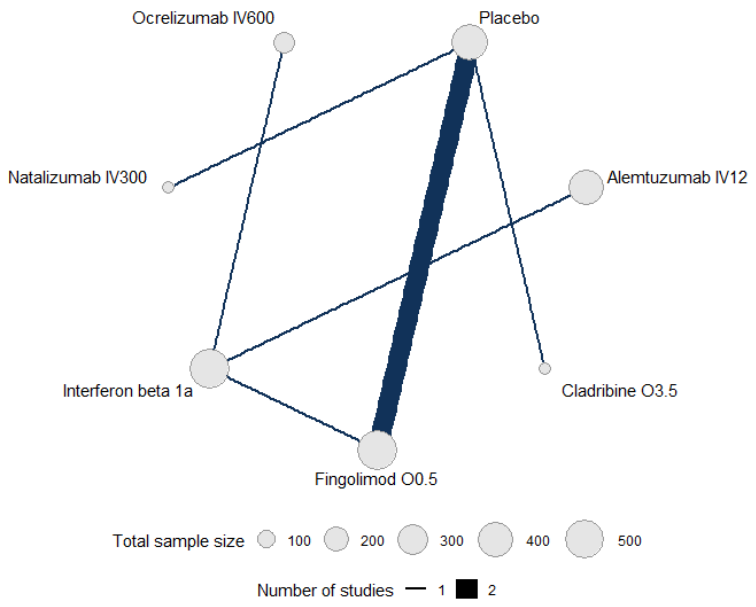
# Efficacy, costs, and utilities

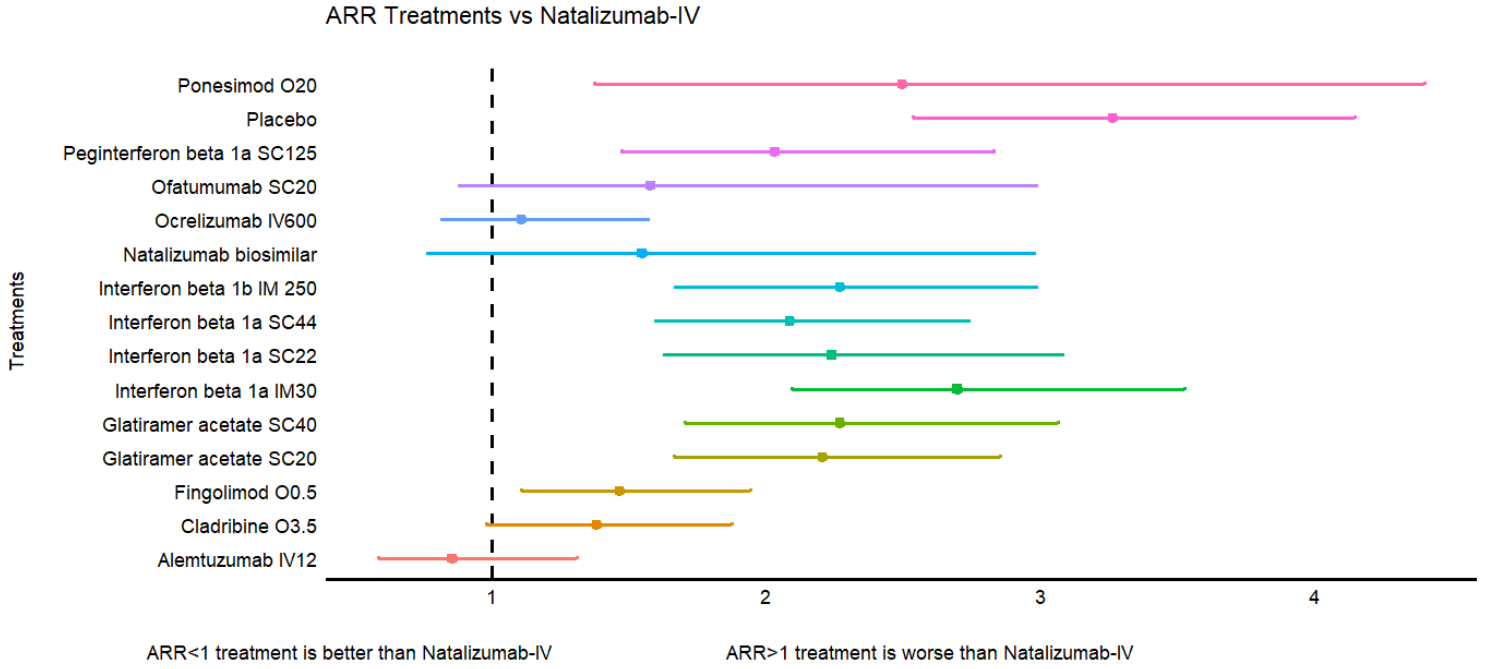
# Confirmed Disease Progression 6months (CDP6)



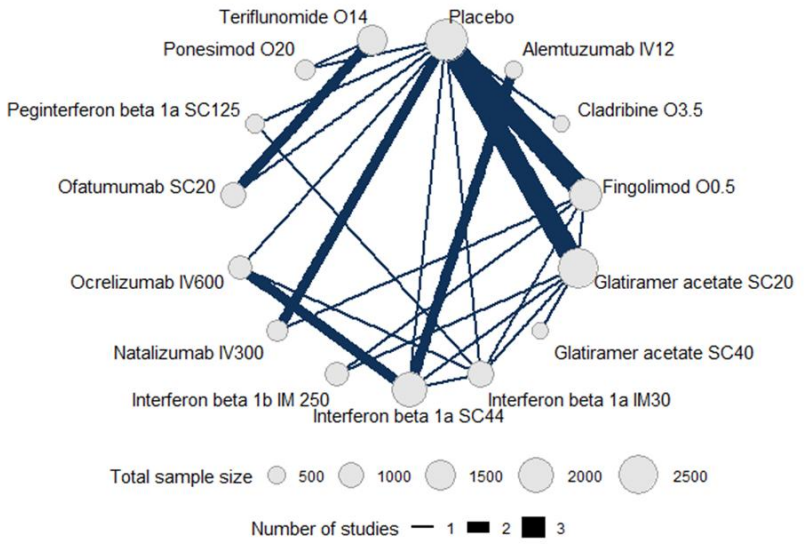



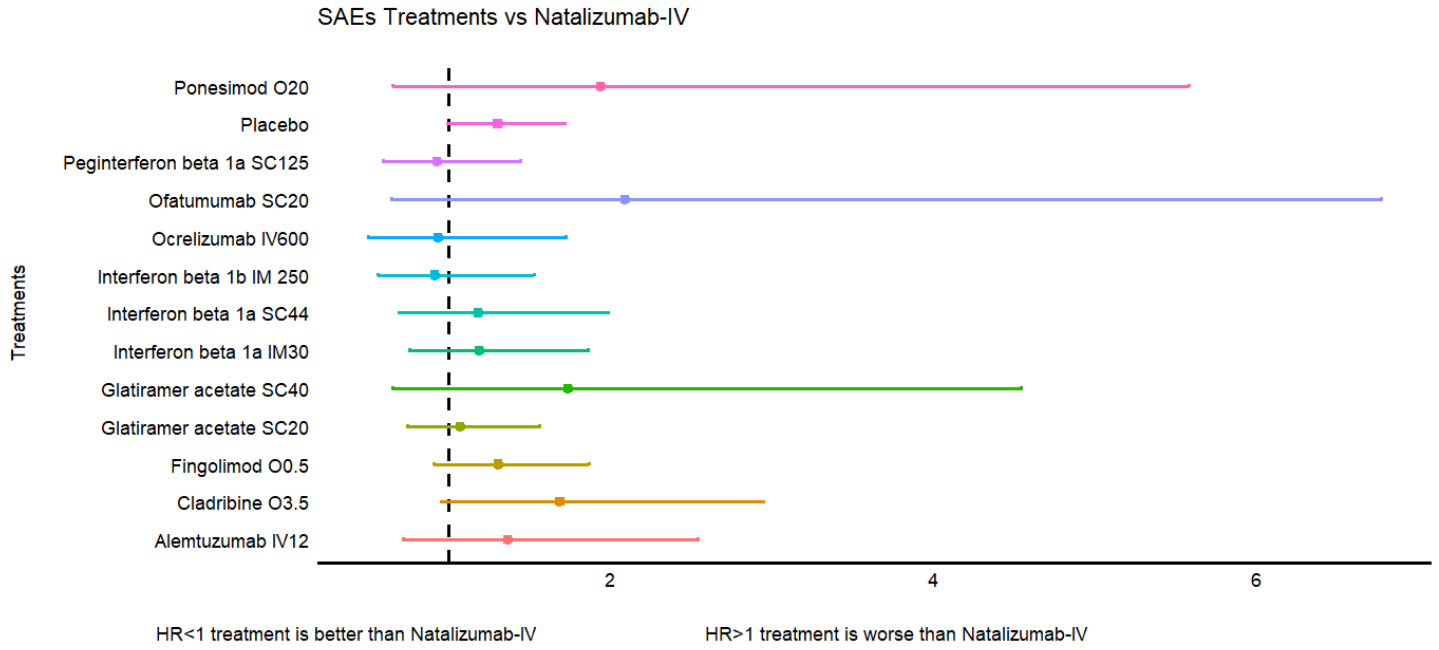
# Annual Relapse Rate (ARR)



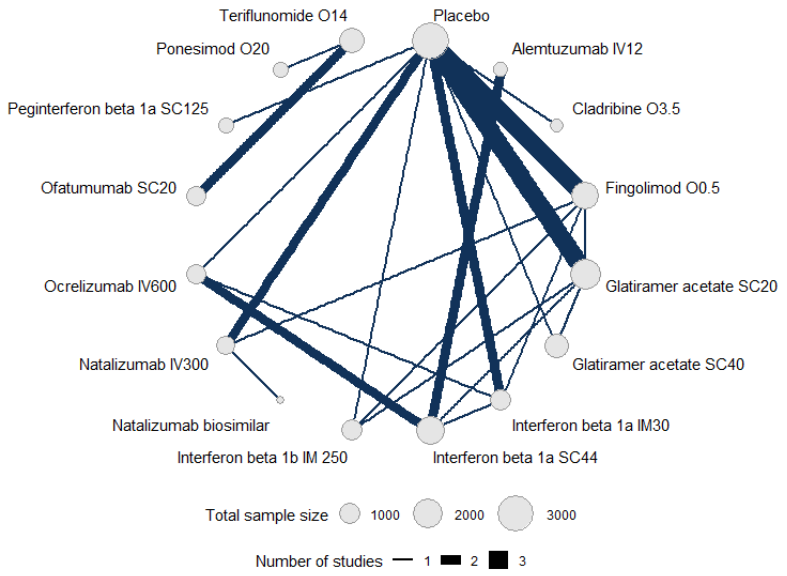



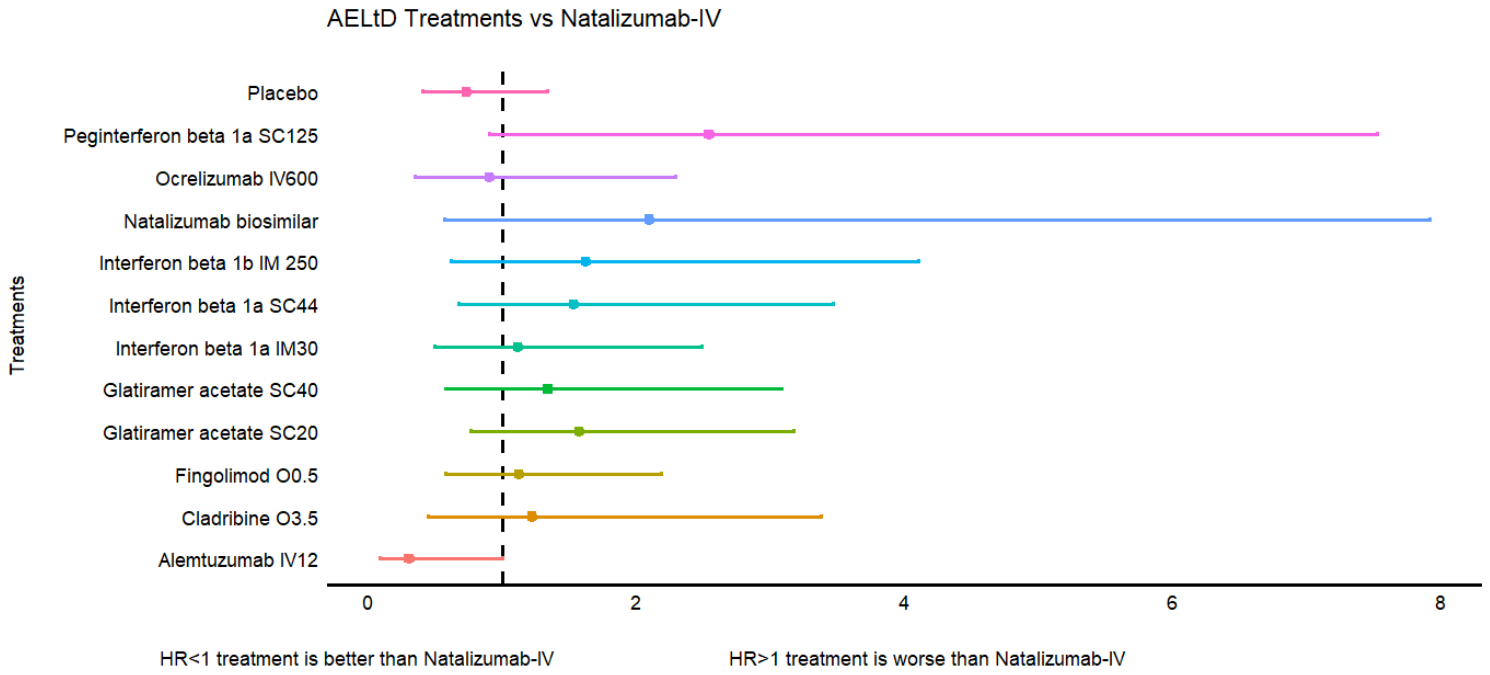
# Serious Adverse Events (SAEs)



# Adverse Events leading to Discontinuation (AEltD)



# Health Related Quality of Life

UK MS Survey 2005

- RRMS utility by severity
- SPMS utility by severity
- Relapse disutility does not vary by severity

Miscellaneous sources

- SAEs disutilities
- Carer disutilities

# Costs

- Annual Treatment acquisition Costs
- Re-treatment beyond years 1 &2 (% informed by clinical opinion)
- Annual Administration & Monitoring Costs
- Annual Treatment Health state costs by  stratified by severity (EDSS)
- Relapse costs vary according to severity (Hospitalisation) but not EDSS

# Implementation with DESCEM

# Setting up & running the model in DESCEM (Warden)

- 2nd and 3rd line treatments
- Importing the data
- Setting Common inputs, deterministic, probabilistic (conditional on age, disease, severity):
  - Baseline characteristics, Natural History, Treatment effects, Mortality, Costs, Utilities
- Unique patient inputs are flags which tracked age, sex, disease type, progression, death, number of events (Treatments, Replaces, treatment switches,) and time (annually, spent in severity states, spent on treatment)
- Initial Events
- Reaction Events
- Discounting
- No of Simulations.

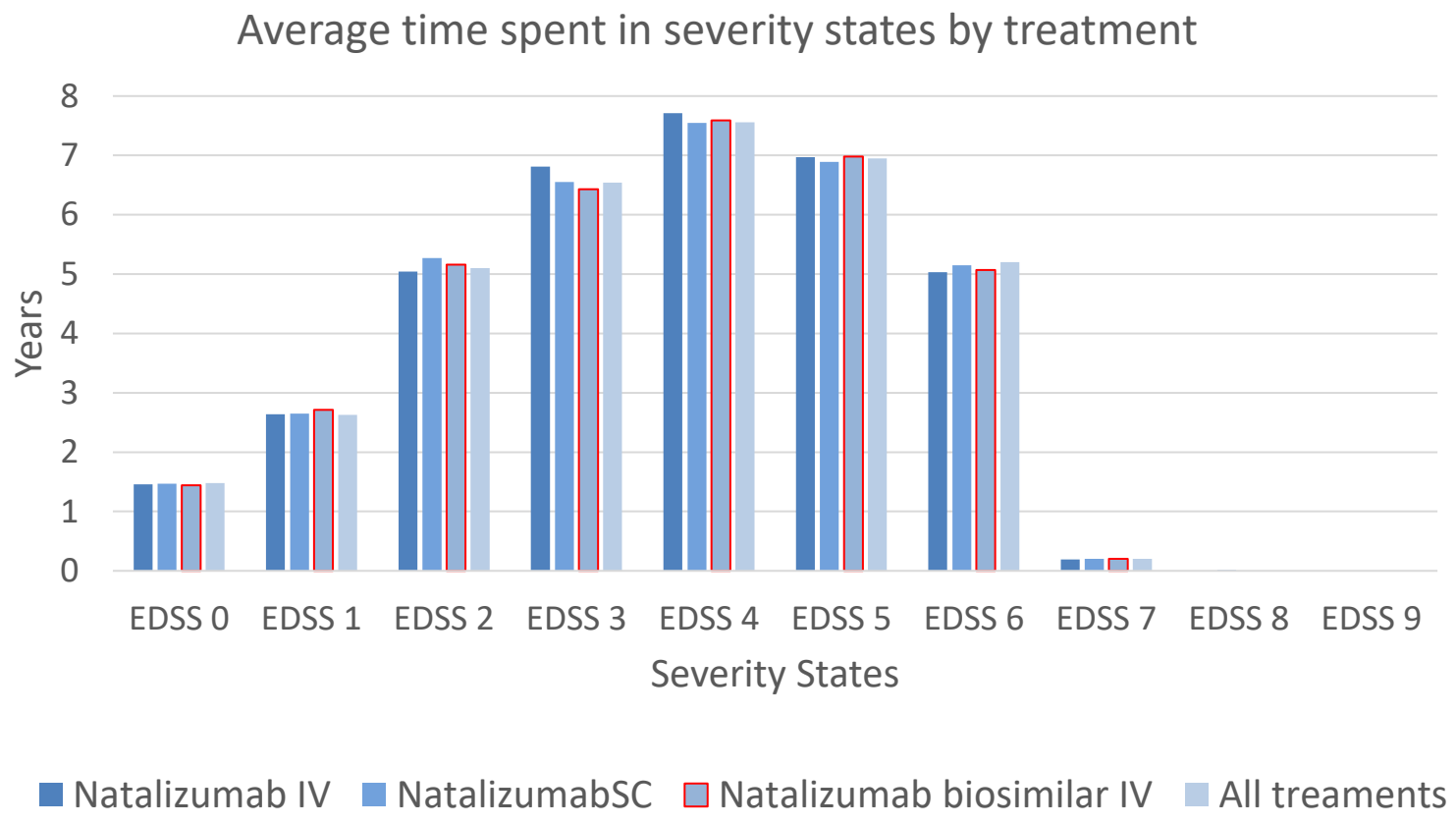
# Results

*publicly available list prices*

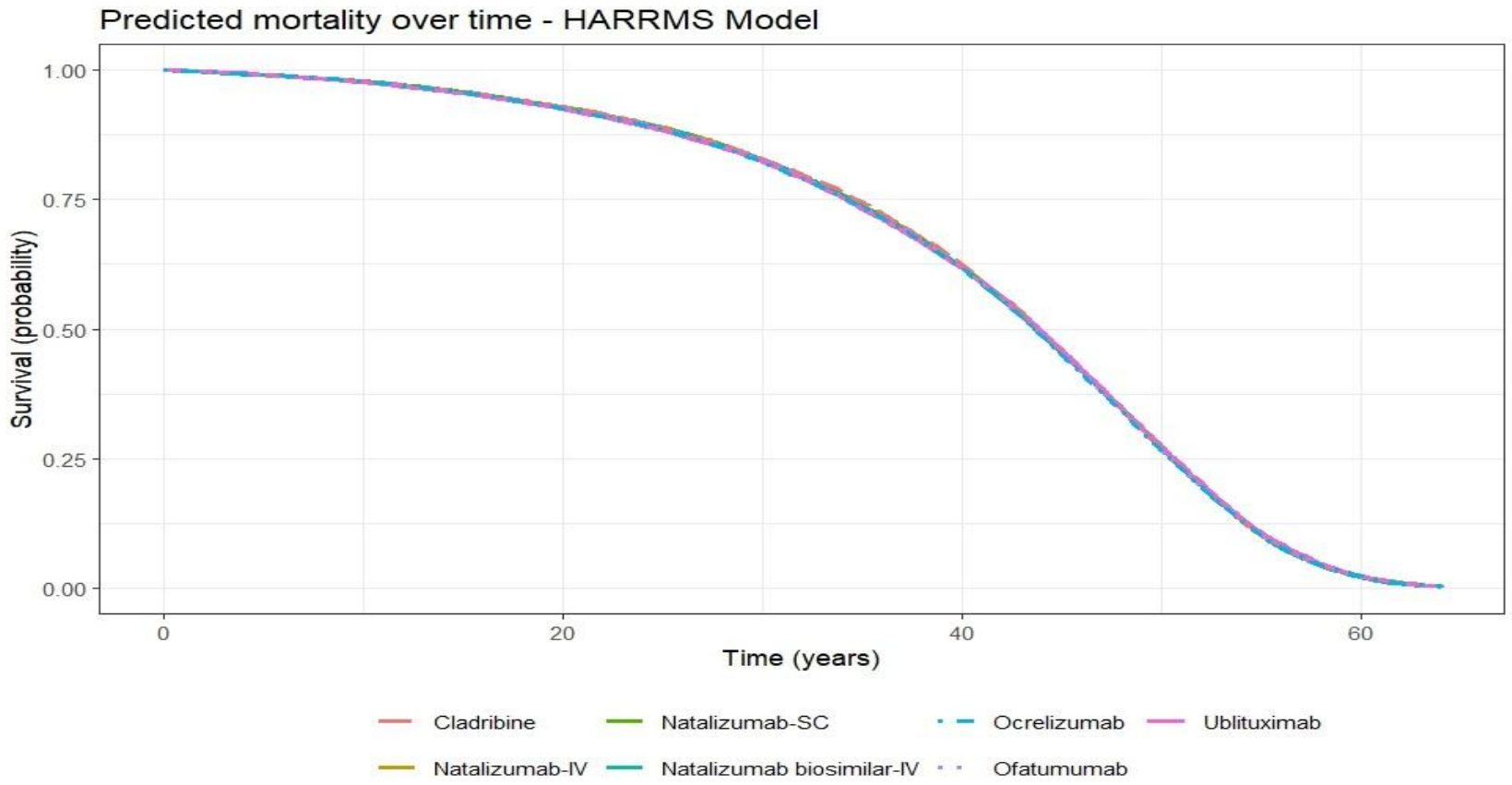
# Validation – average time

| | Natalizumab IV | Natalizumab SC | Natalizumab biosimilar | Average of all treatments |
|---|---|---|---|---|
| Average time to event (years) | | | | |
| Progression | 10.32 | 10.37 | 10.42 | 10.36 |
| Relapse | 10.91 | 11.01 | 10.96 | 10.92 |
| Average time spent on treatment (years) | | | | |
| 2nd line | 9.62 | 9.81 | 9.75 | 9.67 |
| 3rd line | 2.59 | 2.55 | 2.7 | 2.66 |
| 4th line | 1.1 | 1.1 | 1.22 | 1.11 |

# Validation – disease severity over time



# Validation - mortality



# Incremental Costs and QALYs

- High degree of uncertainty
- Difficulty interpreting the results

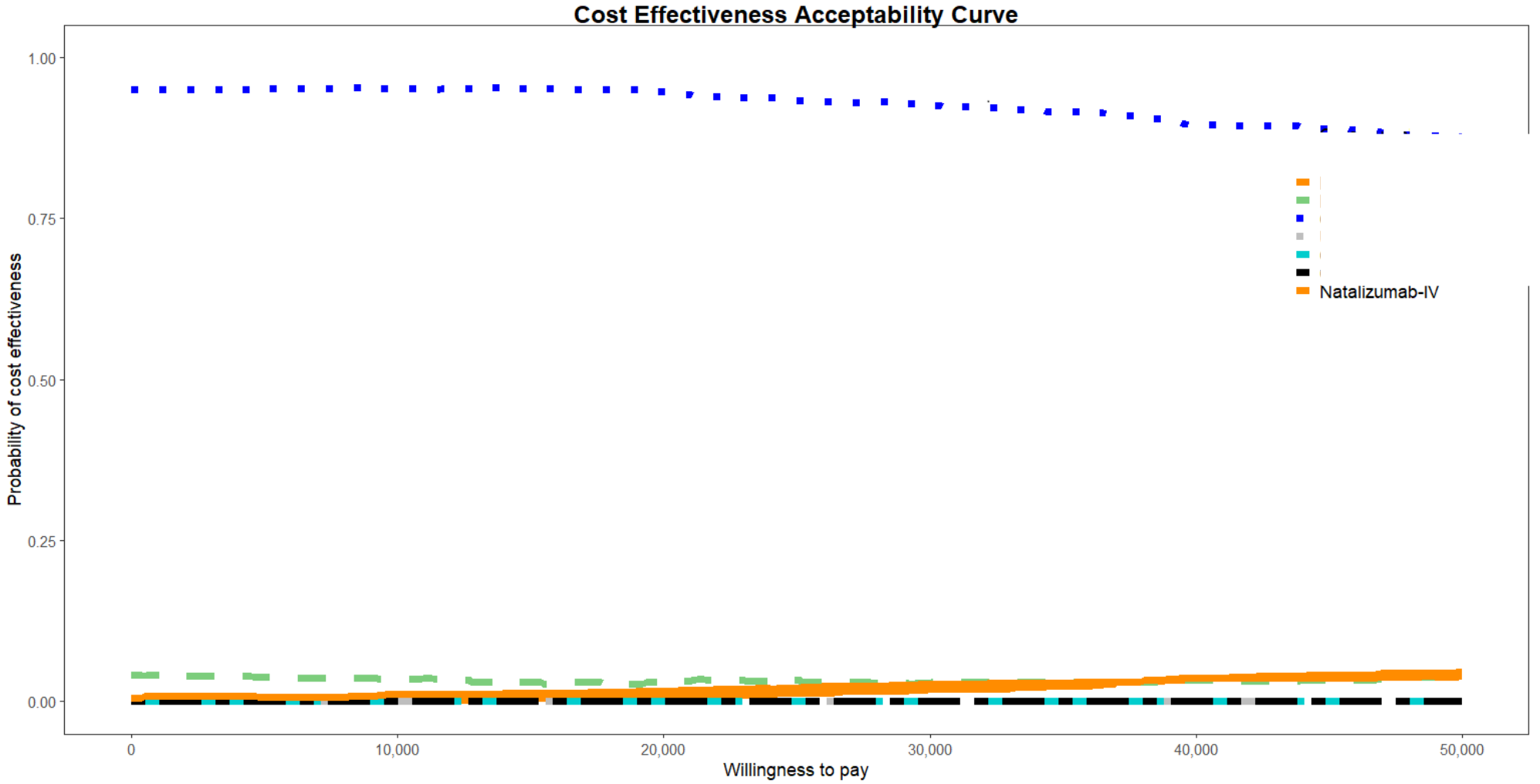
| | Total costs | Total QALYs | Incremental Costs vs Natalizumab-IV | Incremental QALYs vs Natalizumab-IV | ICER |
|---|---|---|---|---|---|
| | 314,000 (271,332, 367,456) | 9.11 (6.72, 11.35) | - | - | - |
| | 314,385 (272,890, 367,079) | 9.12 (6.62, 11.28) | 384 (-12,902, 14,361) | 0.011 (-0.42, 0.42) | 35,030 |
| | 306,705 (264,904, 357,319) | 9.00 (6.65, 11.20) | -7,295 (-21,979, 5,987) | -0.11 (-0.58, 0.34) | 68,821 |
| | 267,751 (231,533, 314,025) | 9.01 (6.55, 11.22) | -46,249 (-108,949, -1,012) | -0.10 (-0.56, 0.36) | 460,503 |
| | 339,848 (294,768, 393,119) | 9.08 (6.76, 11.27) | 25,847 (15,594, 37,457) | -0.03 (-0.51, 0.41) | -857,053 |
| | 329,510 (281,371, 387,638) | 8.94 (6.43, 11.11) | 15,509 (3,469, 30,475) | -0.17 (-0.77, 0.30) | -90,899 |
| | 341,567 (286,838, 406,773) | 9.08 (6.69, 11.26) | 27,567 (7,338, 53,607) | -0.025 (-0.47, 0.37) | -1,119,370 |

# Incremental Net Benefits

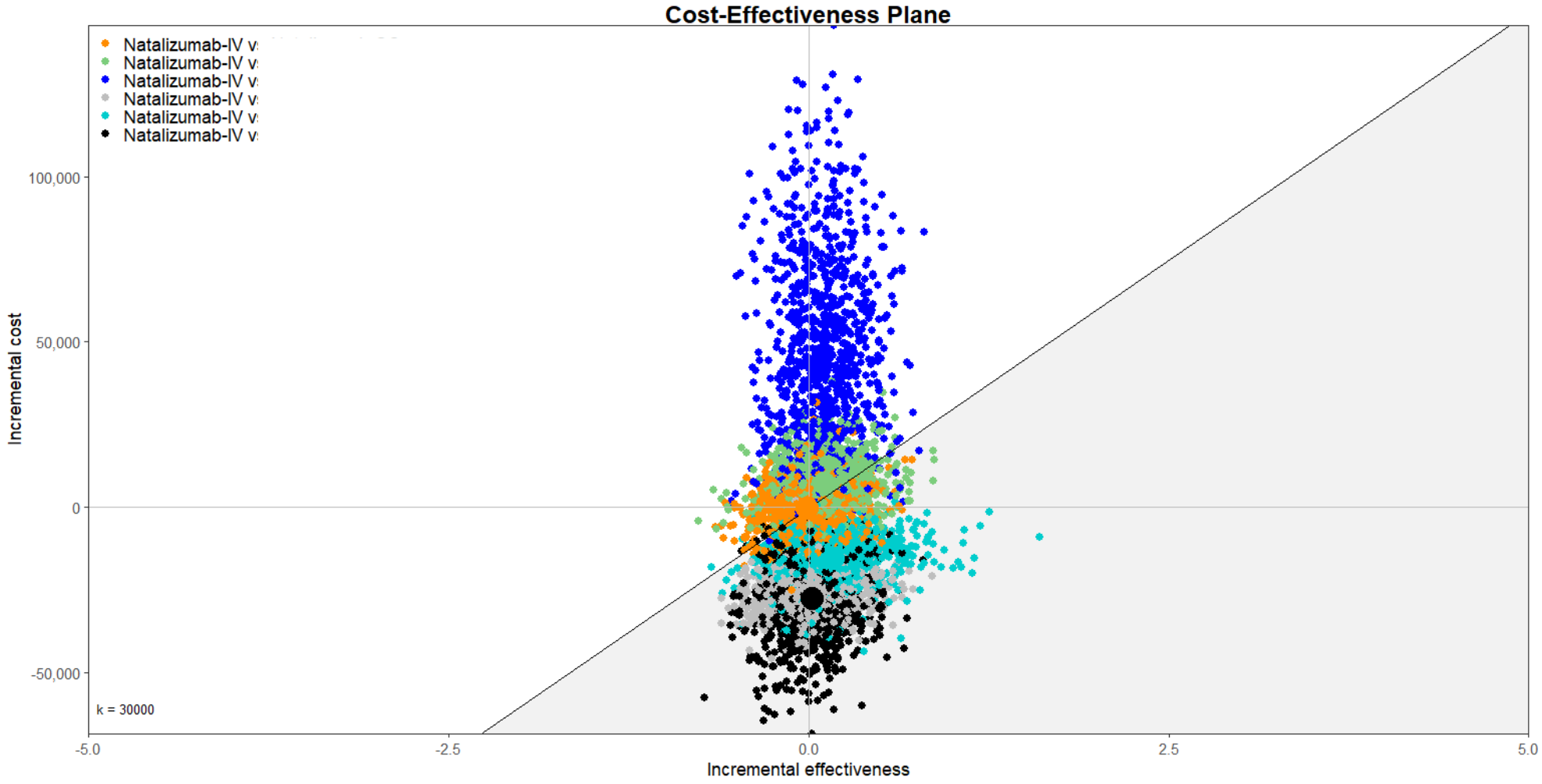
- Preferred due to high uncertainly
- Less familiar to decision makers

| | Net Benefit £20,000 /QALY | Net Benefit £30,000 /QALY | Incremental Net Benefit £20,000 /QALY vs Natalizumab-IV | Incremental Net Benefit £30,000 /QALY vs Natalizumab-IV |
|---|---|---|---|---|
| | -131,808 (-183,657, -90,700) | -40,712 (-107,342, 13,831) | - | - |
| | -131,973 (-181,558, -89,274) | -40,767 (-106,749, 14,312) | -165 (-14,983, 13,741) | -55 (-17,007, 15,910) |
| | -126,633 (-176,162, -86,945) | -36,597 (-96,754, 16,082) | 5,175 (-10,437, 20,970) | 4,115 (-13,996, 21,881) |
| | -87,567 (-148,860, -34,473) | 2,524 (-81,946, 72,046) | 44,241 (-1,540, 109,189) | 43,236 (-2,764, 109,436) |
| | -158,259 (-209,061, -114,561) | -67,464 (-138,206, -11,243) | -26,450 (-39,882, -13,563) | -26,752 (-42,754, -11,095) |
| | -150,730 (-204,786, -104,009) | -61,340 (-132,400, -2,091) | -18,922 (-36,581, -3,897) | -20,628 (-40,070, -2,563) |
| | -159,868 (-216,480, -106,521) | -69,018 (-138,390, -2,917) | -28,060 (-51,876, -6,623) | -28,306 (-53,646, -4,532) |

# CEAC


Cost Effectiveness Acceptability Curve
Probability of cost effectiveness
1.00
0.75
0.50
0.25
0.00
0
10,000
20,000
30,000
40,000
50,000
Willingness to pay
Natalizumab-IV

# CEP


Cost-Effectiveness Plane
Natalizumab-IV v
Natalizumab-IV v
Natalizumab-IV v
Natalizumab-IV v
Natalizumab-IV v
Natalizumab-IV v
100,000
50,000
0
-50,000
Incremental cost
k = 30000
-5.0
-2.5
0.0
2.5
5.0
Incremental effectiveness

# Learnings/Conclusions

# Conclusions/Learnings

- Pros
  - DESCEM (Warden) is rapid way to build of a DES model
  - Workflow in R integrates well with other teams / GitHub
  - Transparent and well received by committee members
- Cons
  - Computationally intensive
  - In accessible non-R users
  - Was difficult to modularise

# Q&A

- Bristol TAG https://www.bristol.ac.uk/population-health-sciences/centres/beam-centre/bristol-tag/
- MULTI NMA https://dmphillippo.github.io/multinma/
- Project https://www.nice.org.uk/guidance/indevelopment/gid-ta10977/
- WARDEN https://jsanchezalv.github.io/WARDEN/
- Detailed presentation to be given at Health Economic Bristol University Modelling Group (HEMBUG), please sign up to our mailing list by emailing ayman.sadek@bristol.ac.uk

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# Discrete event simulation (DES)

- Individual patients characterised by their **attributes**
  - Can include demographics (age, gender), risk factors (EDSS severity), and event history (previous treatments, number of relapses)
- No cycle length as model is continuous time
- Computationally intensive as need (say) 1000 patients for each 1000 probabilistic model run
- But much greater flexibility  to reflect treatment sequences, patient history and utilise new MS Registry analyses

# Value of information analysis

# Title

- Point 1
- Point 2