Project plan:

Health Technology Assessment of medicines, including rituximab, used for primary progressive multiple sclerosis (PPMS).

Project number	ID2019_018
Plan prepared (dd.mm.åååå):	26.03.2019

Short description and summary

Multiple sclerosis (MS) is an immune-mediated inflammatory disease of the central nervous system characterized by demyelination and axonal degeneration.

According to an advisory committee on clinical trials in multiple sclerosis, MS is classified in four different categories (1) including clinical isolated syndrome (CIS), relapsing-remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS).

Currently, among all the medicines that have marketing authorization for the treatment of RRMS, only ocrelizumab has marketing authorisation for both RRMS and PPMS.

In the present Health Technology Assessment (HTA) we aim to exam the clinical and cost effectiveness of RRMS medicines in the treatment of patients with PPMS. We will also include one medicine, rituximab, without marketing authorisation for MS. We will not assess the safety of the treatments as this is considered covered in the *Health Technology Assessment of medicines used for multiple sclerosis. Part I: RRMS.*

Kort beskrivelse og oppsummering

Multippel sklerose (MS) er en immunmediert inflammatorisk sykdom i sentralnervesystemet karakterisert av demyelinisering og aksonal degenerasjon.

En rådgivende komite for kliniske studier om MS, har klassifisert sykdommen i fire kategorier (1): klinisk isolert syndrom (clinically isolated syndrome, CIS), attakvis MS (relapse remitting MS, RRMS), primær progressiv MS (primary progressive MS, PPMS) og sekundær progressiv MS (secondary progressive MS, SPMS).

Blant alle legemidler som har markedsføringstillatelse for behandling av RRMS, er det bare ocrelizumab som har markedsføringstillatelse for både RRMS og PPMS.

I denne metodevurderingen vil vi undersøke klinisk effekt og kostnadseffektivitet for RRMS legemidler i behandling av pasienter med PPMS. Vi inkluderer rituximab som ikke har markedsføringstillatelse for noen av MS-formene, men som blir brukt off-label i MS-pasienter. Vi vil ikke undersøke sikkerheten da vi vurderer at dette vil være dekket av *Health Technology Assessment of medicines used for multiple sclerosis. Part I: RRMS.*

Project category and commissioner	
Product (program area)	Health Technology Assessment
Thematic areas	Drug Multiple Sclerosis Health Technology Assessment
Commissioner:	The Regional Health Authorities Forum (RHA Forum) (Bestillerforum RHF), consisting of the four medical directors (one for each regional health authority) and two delegates from the Norwegian Directorate of Health, and have the mandate to prioritize the single technology assessments (STA) and health technology assessments (HTA) to be conducted on the basis of submitted proposals and horizon scanning reports.
Project management and participants	
Project manager	Torunn E. Tjelle
Responsible for the project	Atle Fretheim
Internal project participants	Ingrid Kristine Ohm Chris Rose Elisabeth Hafstad Gunhild Hagen Vida Hamidi
External project participants	Lars Bø, MD, Helse Bergen Trygve Holmøy, MD, Ahus/UiO Elisabeth Gulowsen Celius, MD, OUS/UiO Rune Midgard, MD, Molde og Ålesund
Plan for replacement by project participants' absence	Replacements will be decided by the person responsible for the project
Internal reviewers of report	To be decided
External reviewers of report	To be decided

Mandate

The national system for managed introduction of new methods in the specialist health services (*Nasjonalt system for innføring av nye metoder i spesialisthelsetjenesten*)

commissioned a comprehensive Health Technology Assessment (HTA) to compare different disease modifying medicines in use for primary progressive multiple sclerosis (PPMS).

Goal

To compare the effect and cost-effectiveness of the disease modifying medicines used for the treatment of patients with PPMS in Norway.

Background

Multiple sclerosis (MS) is an immune-mediated inflammatory disease of the central nervous system characterized by demyelination and axonal degeneration.

According to an advisory committee on clinical trials in multiple sclerosis, MS is classified in four different categories (1) including clinical isolated syndrome (CIS), relapsing-remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS).

Currently, among all the medicines that have marketing authorization for the treatment of RRMS, only ocrelizumab has marketing authorisation for both RRMS and PPMS.

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Methods

We will perform a HTA according to the handbook of Norwegian Institute of Public Health.

Search strategy

The literature searches will be performed by an information specialists using peer-reviewed search strategies. We will search for randomized controlled trials and non-randomised controlled trials according to a set inclusion criteria. The search will be performed using the medicines' generic name.

We will systematically search the literature using the following databases:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- Embase

The information specialist will conduct the literature searches using index terms (Medical Subject Headings and EMTREE terms), and free text terms related to the population and the interventions of interest. The search will be conducted from inception to May 2019 and supplemented with hand searches of selected publications.

Publications selection process

Pairs of independent researchers will select studies in two steps: they will first screen title and abstracts, and full text. In case of disagreement, researches will revise for clarity and involve a third researcher to settle the disagreement.

Assessment of methodological quality and risk of bias

Included RCTs will be assessed for possible risk of bias using the Cochrane Collaboration tool for assessing risk of bias. Risk of bias will be rated as low risk of bias, unclear risk of bias, or high risk of bias. For non-randomised studies we used a checklist for cohort studies from the Handbook of Norwegian Institute of Public health {Folkehelseinstituttet., 2014 #472}.

Inclusion criteria

Population	Men and women aged 18 and above diagnosed with multiple sclerosis. The eligible multiple sclerosis diagnosis is primary progressive multiple sclerosis (PPMS*). ** Definition: at least one year of disease progression and characteristic findings on MRI and/or positive findings in cerebrospinal fluid.*
Intervention	Ocrelizumab, the only disease modifying treatment with marketing authorisation for PPMS, rituximab, and all* MS disease modifying treatment medicines with marketing authorisation for RRMS. ** Alemtuzumab, dimetylfumarat, fingolimod, glatirameracetet, natalizumab, teriflunomide, cladribine, interferon beta 1a (Avonex, Rebif), peg-interferon beta-1a, interferon beta-1b (Betaferon, Extavia)*
Comparisons	Medicines listed above or placebo
Outcome	Disability progression measured using the expanded disability status scale (EDSS) (Safety outcomes will not be assessed: first, we do not expect to find sufficient data, second, we consider safety issues to be sufficiently similar for PPMS and RRMS, which is assessed elsewhere).
Study design	Randomized controlled trials and non-randomised studies.

Exclusion criteria

Treatment of pregnant women. Safety (considered covered by the HTA for RRMS).

Data collection and analyses

Data extraction

One researcher will extract the data from the selected publications. A second will verify the data.

The following data will be extracted:

- Information on publication (author names, year of publication)
- Description of study (design and setting, clinical trial identification, source of funding)
- Participant characteristics and potential confounding factors (number of participants in the trial, age, gender, MS diagnosis, length of disease, and status of disease
- Description of intervention and comparator (i.e. dose, frequency)
- Outcomes, including length of follow-up

Data analyses

If available, we will analyse and present disability progression as a relative risk (RR) or odds ratio (OR), or as a mean difference (MD) in EDSS score from baseline.

We will present meta-analysis results as tables and/or forest plots showing point estimates and summaries of the uncertainty on such estimates. Uncertainty will be presented as 95% confidence intervals (CI; for meta-analyses) or 95% credible intervals (CrI; for Bayesian analyses). If meta-analysis is not possible we will present the results in narrative form.

Grading the certainty of evidence

Pair of researchers will independently assess the certainty of the evidence. We will evaluate the certainty of the evidence using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach (3), using the following definitions:

Grade	Definition
High certainty	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different
Low certainty	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Economic evaluation

In order to assess the cost-effectiveness of the different medicines used for MS, we will update the previously developed probabilistic Markov decision analytic model used for RRMS (4). Analysis will be performed based on net prices of medicines and EDSS estimates from the report. Structure, assumptions and input in the previously developed health economic model may be considered modified if we receive feedback that the project group considers highly relevant.

Other stakeholder involvement

We will contact Sykehusinnkjøp for input on relevance of the different medicines and all manufacturers of the included medicines for input on effect data or for their considerations of the HTA as such.

Norwegian Institute of Public Health review process

We follow the process of Norwegian Institute of Public Health (NIPH) where two external clinical experts and two internal research directors are invited to review and give feedback on the project plan. The plan will then be approved by an internal group at NIPH before publication at NyeMetoder.no. The final report will be reviewed by another two external experts together with the same two internal research directors. Subsequently it will be approved by an internal group at NIPH before submission to the commissioner.
Publication (https://nyemetoder.no/metoder), will be done latest 10 days after submission to the commissioner.

Activities and schedule

Following activities are planned in the project, and presented in a Gantt diagram.

Task	Responsible	Calendar time (days)	End date
Find and include external reviewers, same as for RRMS	Tjelle		Done
Discuss project plan with internal and external reviewers (external reviewers: on email)	Tjelle	10	March 2019
Peer-review and approval of project plan	Heads of Departments	5	March 2019
Search literature	Harboe/Hafstad	5	March 2019
Select studies according to inclusion/exclusion criteria	Tjelle	15	June 2019
Evaluate the methodological quality (RoB)	Tjelle	5	June 2019
Extract data on efficacy and safety and conduct statistical analyses	Tjelle	10	August 2019
GRADE evaluation for each outcome	Tjelle	10	August 2019
Construct/update economic model: same model as for RRMS			Done
Gather data and run economic model		30	September 2019
Write and review draft report	Tjelle	20	September 2019
Input from internal and external reviewers	Tjelle	14	September 2019
Approve and submit the report	Heads of Departments	10	September 2019

Dates

Date for commission: January 2019
Start date at NIPH: March 2019
End date: September 2019

Publication / dissemination

The HTA report will be published as a NIPH report (in English), and possibly also as a scientific publication in a widely distribute journal to reach international readers. Abstracts may be submitted to selected conferences.

References

1. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sorensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014;83(3):278-86. doi: 10.1212/WNL.0000000000000560. Epub 2014 May 28.
2. Cochrane Effective Practice and Organisation of Care (EPOC). Suggested risk of bias criteria for EPOC reviews. EPOC Resources fo r review authors, 2017.[cited]. Available from: https://epoc.cochrane.org/resources/epoc-resources-review-authors
3. Puhan MA, Schunemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ (Clinical research ed) 2014;349:g5630.
4. Couto E, Hamidi V, Ringerike T, Odgaard-Jensen J, Harboe I, Klemp M. NIPH Systematic Reviews. In: Medicines Used for Multiple Sclerosis - A Health Technology Assessment. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH); 2016.