folkehelseinstituttet

Project plan:

Health Technology Assessment of medicines used for multiple sclerosis. Part I: RRMS

An update and substantial extension of
"1030 Medicines used for Multiple Scleroses – A Health Technology Assessment"

Project number	ID2018_004
Plan prepared (dd.mm.yyyy)	10.09.2018
Amendment prepared (dd.mm.yyyy), see pp 13	01.02.2019

Short description and summary

Multiple sclerosis (MS) is a chronic, inflammatory disease affecting the central nervous system (CNS). The symptoms depend on the location of the lesions in the CNS. The prevalence rate for multiple sclerosis in Norway is among the highest reported worldwide. This disease, which usually starts around the age of 30 (range 20-40), most commonly has a relapsing-remitting course in about half the patients, followed by a secondary progressive phase. Most patients experience increasing disability involving motor, sensory, visual, and bowel and bladder systems. The medicines used today in patients with signs or symptoms of inflammation are disease-modifying drugs. In 2016 the NIPH conducted a Health Technology Assessment (HTA), including a network meta-analyses, on 11 different medicines

(https://nyemetoder.no/metoder/multippel-sklerose-ms-fullstendig-metodevurdering).

The present Health Technology Assessment (HTA) have added two new medicines for the indication and removed a group of medicines (interferons) due to low priority use. We also included one medicine without marketing authorisation, rituximab (a drug with marketing authorisation for rheumatoid arthritis, B cell non-Hodgins's lymphomas and a few types of cancer), which is used off-label in MS-patients. We aim at examining the relative effect, safety and cost-effectiveness of these medicines used for multiple sclerosis in Norway. The report will also assess the legal and ethical implications using rituximab off-label.

Kort beskrivelse og oppsummering

Multippel sklerose (MS) er en kronisk, inflammatorisk sykdom som berører sentralnervesystemet (CNS). Symptomene er avhengig av lokalisasjonen av lesjonene i CNS. Hyppigheten av MS i Norge er blant de høyeste i verden. Sykdommen starter vanligvis i 30-årsalderen og viser seg i form av gjentagende anfall (attakker) i omtrent 50% av pasientene: dette utvikler seg deretter til en sekundær progressiv fase. De fleste pasientene opplever økt funksjonshemming som inkluderer motorisk, sensorisk, visuell og tarm- og blære-systemer.

Dagens medisiner som blir brukt på pasienter med tegn eller symptomer på betennelse er sykdomsmodifiserende medisiner. I 2016 utførte FHI en metodevurdering med nettverksanalyse på 11 forskjellige medisiner.
I den nye metodevurderingen vi nå gjør har vi inkludert to nye medisiner for MS. Vi har også fjernet en gruppe medisiner (interferonene) som var med i forrige rapport på grunn av at bruken av disse har lav prioritet. I tillegg har vi inkludert en medisin, rituximab, uten markedsføringstillatelse for MS, men som blir brukt "off-label" for denne indikasjonen. Rituximab er registrert for reumatoid artritt, B-celle non-Hodgins lymfom og noen andre krefttyper. Vi vil undersøke relativ effekt, sikkerhet og kostnadseffektivitet av disse medisinene i Norge. Rapporten vil også inkludere juridiske og etiske vurderinger for bruk av rituximab som et off-label medikament.

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 has 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	Lene K Juvet
Internal project participants	Gunhild Hagen Ingrid Harboe Elisabet Hafstad Lise Lund Håheim Christopher J. Rose Ulrikke Højslev Lund Eva Pike Julia Bidonde
External project participants	**Effect and safety:** Lars Bø, MD, Helse Bergen Trygve Holmøy, MD, Ahus/UiO Elisabeth Gulowsen Celius, MD, OUS/UiO Rune Midgard, MD, Molde og Ålesund **Law and ethics:** To be decided
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*) commisioned a comprehensive Health Technology Assessment (HTA) to compare different disease modifying medicines in use for multiple sclerosis.

Goal

- To compare the effect, safety and cost-effectiveness of the disease modifying medicines used for multiple sclerosis in Norway, including rituximab as an off-label drug used for the indication.
- To evaluate legal and ethical perspectives using an off-label drug for an indication where registered drugs are available.

Background

Multiple sclerosis is a chronic, inflammatory disease affecting the central nervous system (CNS). The symptoms depend on the location of the lesions in the CNS (1). There are many symptoms and signs of the disease, typically motor, sensory, visual, and bowel and bladder symptoms (1).
Multiple sclerosis (MS) is more common among women than men (2). The Norwegian MS prevalence rate is among the highest reported worldwide (1;3). A study, using the National Patient Registry (NPR), Oslo MS Registry and the Norwegian MS Registry and Biobank, estimated a national prevalence rate of 203/100, 000 (3).
The disease usually starts around the age of 30 (range 20-40). In 10-15% of MS patients, the illness is progressive from onset (1). In most patients the disease initially has a relapsing-remitting course that can last several years. With time, recovery from each episode is incomplete and persistent symptoms accumulate (1). Around 65% of relapsing-remitting patients evolve to a phase of increasing dysfunction (secondary progressive phase) (1).
Medicines in use are disease modifying drugs that inhibit the inflammatory process, and aim to prevent progression and reduce disability.

Methods

We will perform a health technology assessment (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. Three searches will be performed for identifying potential studies (see details for study design under "Inclusion criteria"):

1. An updated search based on the previous Norwegian HTA (4). We will limit the search to year of publication 2015-2018. The medicines that will be included are listed under "Inclusion criteria".
2. A full search of medicines not included in the previous HTA. No date limitation.

3. A full search of the use of rituximab as a disease modifying drug for multiple sclerosis. No date limitation.

All searches will be performed using the generic name of the medicines.

We will systematically search the literature using the following databases:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- Embase
- Cochrane Library; Cochrane Database of Systematic Reviews, Other Reviews, Technology Assessments, Cochrane Central Register of Controlled Trials (Central)
- Centre for Reviews and Dissemination; DARE, HTA
- ISI Web of Science
- PubMed (epub ahead of print)
- Epistemonikos
- EUnetHTA POP database (POP = Planned and Ongoing Projects)
- PROSPERO – Centre for Reviews and Dissemination
- WHO ICTRP
- ClinicalTrials.gov

We will hand search the following websites:

- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Agency for Healthcare Research and Quality (AHRQ),
- FinOHTA - Finnish Office for Health Technology Assessment
- Statens beredning för medicinsk og social utvärdering (SBU)

The research librarian/information specialist (in collaboration with the project team) will conduct the literature search using index terms (Medical Subject Headings and EMTREE terms), and free text terms related to the population and the interventions of interest. All retrieved records published in the period covered by these databases until the date of search will be considered. The search will be supplemented with relevant papers found in bibliographies of selected publications. We will search for and identify relevant ongoing or unpublished trials.

Publications selection process

We will select studies that will be included in the HTA through two steps. In both steps, two persons will work independently considering inclusion criteria. In the first step, these two persons will read all titles and abstracts retrieved by the literature search and select possible relevant full-texts. In the second step, the persons will read all the selected full text articles to decide which articles should be included in the HTA. In both steps, 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

Individual 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 the ROBINS-I tool (Risk of Bias in non-randomized studies – of interventions) will be used.

Inclusion and exclusion criteria

Inclusion criteria

Population

Men and women aged 18 and above diagnosed with multiple sclerosis. The eligible multiple sclerosis diagnosis is relapse-remitting multiple sclerosis (RRMS*) (as for the previous report) who are treatment naïve or not, at the start of the trial.

** Definition: objectively established disease with two or more clinical attacks (also called relapses or exacerbations) and localisation of two or more lesions in the CNS. It is characterised by episodes of acute worsening of function followed by partial or complete recovery.*

Intervention

All disease modifying treatments that have been registered in Nye Metoder (Metodevarsler):

- Medicines included in the previous report (see table below)
- Emerging medicines for the indication (see table below)
- Rituximab (used off-label for the indication)

Generic name	**Delivery method**	**Brand name**	**Distributor in Norway**	**Date of approval for MA[1] for MS in EU**
Medicines included in previous report[2]				
Alemtuzumab	Intra venous (IV)	Lemtrada	Sanofi (Genzyme)	12/09/2013
Dimetylfumarat	Capsules	Tecfidera	Biogen Idec Norway AS	30/01/2014
Fingolimod	Capsules	Gilenya	Novartis	17/03/2011
Glatirameracetat	Sub cutaneous (SC)	Copaxone	Teva Pharma AG	Not found
Natalizumab	IV	Tysabri	Biogen Idec Norway AS	27/06/2006
Teriflunomide	Film coated tablets	Aubagio	Sanofi (Genzyme)	26/08/2013
Emerging medicines				
Cladribine/Kladribin	Tablets	Mavenclad	Merc Serono	22/08/2017
Ocrelizumab	IV	Ocrevus	Roche Norge AS	08/01/2018
Off-label used medicines[3]				
Rituximab	IV	MabThera Rixathon	Roche Norge AS Sandoz	No approval for MS

1 MA, Marketing approval
2 Interferons, including peg-interferon, have been excluded, see exclusion criteria.
3 Skilarence (from Almirall S.A.), a drug with MA for psoriasis, has been identified as used off-label for MS. However, its active constituent (dimeylfumarat) is used in other drugs with MA for MS. If found in searches on dimetylfumarat, these studies will be included if otherwise eligible. It will not be performed a separate search on this brand name.

Comparisons

- Medicines in the list, interferons or placebo
- For rituximab we also accept no comparator (as single group, panel or MS registry data studies)

Primary outcomes

- Number of clinical relapses
- Disability progression measured using the expanded disability status scale (EDSS), including information on duration of follow up
- Mortality
- Serious adverse events, as defined by Food and Drug Administration (FDA) (5)
- Lesions detected using Magnetic Resonance Imaging (MRI)

Secondary outcomes

- Withdrawal from study due to adverse events
- Stay at hospital (we will not consider hospital visits)
- Health related quality of life measured with EQ-5D

For the health economy model, we will use the following outcomes

- Annual relapse rate
- Disability progression

Study design

Study designs for the different searches:

- For the updated search (based on the previous Norwegian HTA (4)) and for the new medicines: randomised controlled trials will be included
- For results on safety on rituximab: All study designs will be included, including register studies or panel data
- In addition:
  - We will retrieve systematic reviews and meta-analysis studies to check the included primary studies and references to ensure our search has captured all relevant studies
  - We will identify companion studies and use them to search for updated data
  - We will include studies presenting pooled data, trial extensions, post-hoc analyses and interim analyses to search for the most updated data from relevant primary studies

Exclusion criteria

- Cellular and molecular mechanisms of the drugs.
- D-biotin and daclizumab has been withdrawn from market and is therefore not included.
- All interferons, including peg-interferon, are excluded as interventions due to low-priority use, but will be included as a comparator for other included drugs.
- Rituximab delivered sub cutaneous is excluded since this delivery method has not been used for the present indication.
- Treatment of pregnant women.

Data collection and analyses

Data extraction

One of the two researchers will extract the data from the selected publications. The 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, e.g. by EDSS)
- Description of intervention and comparator (i.e. dose, frequency)
- Outcomes (number of events, methods used to ascertain outcome data, estimates of risk, length of follow-up).

Measures of treatment effect

For the primary outcomes, we will analyse comparisons of:

- number of clinical relapses as an annualized rate ratio (ARRs)
- disability progression as a relative risk (RR) or odds ratio (OR) of progression versus no progression, and as a mean difference (MD) or change in EDSS score
- mortality as an ARR
- serious adverse events as a RR or OR of zero versus one or more serious adverse events
- lesions detected using magnetic resonance imaging as a RR or OR of zero new lesions versus at least one new lesion.

For the secondary outcomes, we will analyse comparisons of:

- study withdrawal due to adverse events as a RR or OR of withdrawal versus no withdrawal
- hospital stay as a MD in number of days
- health-related quality of life as a RR or OR of better health state on at least one dimension and no worse in any other dimension, versus the same or worse health state.

We will use alternative scales if appropriate (e.g., if a continuous outcome has been measured/reported in the included RCTs using different instruments/scales we may use a standardized mean difference; SMD).

If any of the included studies report results for the same participants (e.g., extension studies), we will extract data only for the study with longest follow-up. If any of the included studies use a cross-over design, we will extract data for the first period only, due to possible carry-over effects.

Dealing with missing data

For dichotomous outcomes, we will assume (impute) that participants lost to follow-up experienced the adverse event (e.g., clinical relapse). We will not perform imputation for other outcomes. We will base statistical analyses on the intention to treat principle (all participants analysed in the group to which they were allocated, and all available data included in the analyses).

Statistical analyses and presentation of results

Statistical analyses will only be performed for studies that compare at least two of the included treatments or comparators.

We will judge the possibility of publication bias for each primary outcome using a funnel plot. Because formal statistical tests of funnel plot asymmetry generally lack power, we will not use such tests to exclude the possibility of publication bias (6).

We will conduct a pairwise meta-analysis for each available outcome and each identified intervention vs. control group comparison. We will then perform a network meta-analysis (NMA) for each available outcome. These will be performed by combining direct and indirect estimates of the effect of the interventions of interest for each outcome. We anticipate heterogeneity due to differences between studies and interventions, and will assume a random effects model for all meta-analyses.

For each NMA, we will consider the appropriateness of the transitivity assumption that underpins the approach by exploring, where possible, the distributions of potential treatment effect modifiers (i.e., the variables defined in “Data extraction”, above) among the included studies. If we judge that the inclusion of particular studies will violate the transitivity assumption, we will perform subgroup analysis or network meta-regression (to adjust for potential treatment effect modifiers), or omit those studies from the analysis, or will opt not to perform the NMA if there are too few studies to support analysis. Any studies omitted from any analysis will be reported as such.

For each NMA, we will present the geometry of the network as a figure that shows the direct evidence available (i.e., all pairwise comparisons), and its influence (weight) in the NMA. We will use NMA methods that account for the correlation structure induced by multi-arm trials. We will preferentially use frequentist NMA methods described by Rücker (7), and by Schwarzer et al. (8) using the netmeta R package (version 0.9-8 or later). Briefly, this method poses NMA as a generalized linear model (GLM) whose coefficients are estimated via the Moore-Penrose pseudoinverse of the network’s Laplacian matrix. However, the method will yield biased results if the normal approximation assumed by the model is violated (in particular if there are a substantial number of studies where few or no events were observed) (9), and the netmeta package does not currently permit network meta-regression to be performed.

If there are outcomes for which a substantial number of studies have a low number of events, or if network meta-regression must be performed, we will use a Bayesian NMA approach, such as

the GLM-based framework described by Dias et al. (10), using the gemtc R package (version 0.8-2 or later). This method uses the JAGS Markov Chain Monte Carlo (MCMC) sampler (version 4.3.0 or later; Martyn Plummer, International Agency for Research on Cancer, Lyon, France). Any Bayesian analyses will use binomial likelihoods for dichotomous outcomes or normal likelihoods for continuous outcomes and vague priors on all parameters (11). We will use four MCMC chains with different initializations and conservative numbers of burn-in and posterior samples. We will evaluate the quality of the samples drawn to approximate posterior distributions quantitatively using the potential scale reduction factor, and qualitatively by inspecting diagnostic plots. We will briefly summarize our conclusions about the quality of the samples, but due to the potentially large number of summary values and plots that may result, we may choose to present these in an electronic appendix or omit them, unless their inclusion is deemed particularly informative. If we judge posterior samples to be untrustworthy (e.g., there is poor mixing of the chains) and the problem cannot be solved straightforwardly by changing readily-available options, the NMA will be abandoned.

We will check for inconsistency between direct and indirect evidence by comparing pairwise meta-analysis results with NMA results. We will consider estimates to be inconsistent if their confidence or credible intervals do not overlap. For frequentist NMAs, we will present net heat plots to aid the assessment of inconsistency, will assess network and within- and between-design homogeneity and consistency via decompositions of Cochrane's Q statistic. For frequentist and Bayesian NMAs, we will also assess inconsistency by "node-splitting" (12).

For each primary outcome, we will rank the treatments in terms of their likelihood of leading to the most favourable outcome. For frequentist analyses, we will rank treatments using P-scores (13), which quantify the extent of certainty that one treatment is better than another treatment, averaged over all competing treatments. For any Bayesian analyses, we will rank the treatments using the surface under the cumulative ranking curve (SUCRA) (14). We will interpret the rankings cautiously, taking into account the quality of evidence.

For each primary outcome, where possible, we will perform subgroup, sensitivity, or regression meta-analyses with respect to risk of bias (e.g., all included studies versus those assessed to have low risk of bias), type of intervention (e.g., drug mechanism or category, according to Sykehusinnkjøp's categories), and disease activity (e.g., low versus high activity).

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 frequentist analyses) or 95% credible intervals (CrI; for Bayesian analyses). For Bayesian analyses, we will present point estimates as posterior means or medians and specify which estimate is used. We will consider a result "significant" if the CI or CrI excludes the null value of the scale used (e.g., RR = 1 or MD = 0). Where possible, we will also present results in an interpretable way (e.g., as assumed and corresponding risks).

To the extent that it is practicable, we will use the NMA extension to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) checklist (11) to ensure analyses are performed and reported according to accepted good practices. We will report any

limitations of the analyses, and justify any substantial deviations from this statistical analysis plan.

Grading the certainty of evidence

Two review authors will independently assess the certainty of the evidence for each selected outcome. We will evaluate the certainty of the direct, indirect, and combined evidence from the NMAs using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach (15), 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 (4). Analysis will be performed based on net prices of medicines. Efficacy estimates will be taken from the results of the systematic literature review. 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.

Legal aspects

We will appoint a legal consultant to assess potential legal aspects of using an off-label drug for this indication.

Ethical aspects

We will appoint an ethicists to assess and evaluate ethical aspects of using an off-label drug for this indication.

Other stakeholder involvement

We will contact Sykehusinnkjøp for input on relevance of the different medicines, all manufacturers of the included medicines for input on effect data or for their considerations of the HTA as such, and relevant patient organizations for input on which outcome measures would be important for them. The stakeholders will be included during the process of acquiring data.

Norwegian Institute of Public Health review process

We follow the process of Norwegian Institute of Public Health 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	Start date	Calendar time (days)	End date
Find and include external reviewers	Tjelle	16.05.2018	30	15.06.2018
Discuss project plan with internal and external reviewers	Tjelle/Hagen	16.05.2018	40	25.06.2018
Peer-review and approval of project plan	Heads of Departments	25.08.2018	10	04.09.2018
Search literature	Harboe/Hafstad	20.05.2018	20	09.06.2018
Select studies accodring to inclusion/exclusion criteria	Tjelle	25.07.2018	45	08.09.2018
Evaluate the methodological quality (RoB)	Tjelle	08.09.2018	20	28.09.2018
Extract data on efficacy and safety and conduct statistical analyses	Tjelle/Rose	29.09.2018	50	18.11.2018
GRADE evaluation for each outcome	Tjelle	19.11.2018	14	03.12.2018
Construct/update economic model	Hagen	20.09.2018	24	14.10.2018
Gather data and run economic model	Hagen	18.11.2018	50	07.01.2019
Write and review draft report	Tjelle	07.01.2019	50	26.02.2019
Input from internal and external reviewers	Tjelle/Hagen	27.02.2019	60	28.04.2019
Approve and submit the report	Heads of Departments	29.04.2019	30	29.05.2019

Dates

Date for commission: February 2018
Start date at NIPH: May 2018
End date: May 2019

Publication / dissemination

The HTA report will be published as a NIPH report (in English), and possibly also as a scientific article to reach international readers. Abstracts may be submitted to relevant conferences.

Project plan: AMENDMENT

Changes to the project plan.

We have made the following changes to the plan:

1. Inclusion of registry studies
2. Removal of EQ-5D as an outcome
3. Presenting absolute effect estimates
4. Elaboration of plans for the ethical and legal part of the report
5. Elaboration of plans for user involvement
6. Other changes

1. Inclusion of registry studies

The collection of patient data – especially in national disease registries – facilitates observational studies of the safety and efficacy of treatments used in routine medical practice in large populations. The clinical experts taking part in this HTA were the driving force behind our decision to include registry studies. The rational is that such studies can reflect safety and efficacy in a more realistic setting compared to randomised controlled trials.

However, the inclusion of registry studies poses additional risks of bias, including but not limited to their non-randomized and often retrospective nature. We have therefore modified our search strategy, inclusion and exclusion criteria, and data extraction and analysis plans to address these additional challenges.

Search strategy for registry studies

The literature searches for registry studies of all included drugs will be performed by an information specialist using peer-reviewed search strategies. The searches will be performed in Embase (Ovid), Ovid MEDLINE and Web of Science. We will add subject headings and search terms for registry studies to the subject search (population and interventions) with no limit to year of publication.

Inclusion and exclusion criteria for registry studies

Inclusion criteria:

- Studies retrieving data from national-, regional- or hospital-level registries.
- Studies with retrospective or prospective designs (e.g., chart reviews).
- Studies with comparator.

- Studies of patients diagnosed with RRMS or SPMS, provided the sample analysed in the study reflects the population rate of about 85% RRMS and 15% SPMS. We will not include studies if less than 75% of the included patients had a diagnosis of RRMS.
- Languages: only studies in Latinate or Scandinavian languages, English, or German.

Exclusion criteria:
- Cohort studies not based on registry data.
- Studies based on data retrieved from sources other than registries (e.g., questionnaires sent to participants by researches).

Data extraction

Data will be extracted from multi-arm registry studies as described in the project plan.

Data analyses - general

Data will be analysed as described in the project plan, with the following modifications to facilitate meta-analysis of data extracted both from randomized controlled trials (randomized evidence) and registry studies (non-randomized evidence):

- Where possible, we will perform contrast-based NMA using randomized and non-randomized evidence. We may opt to perform arm-based NMA if we judge that this approach is more practical for modelling the distinction between randomized and non-randomized evidence. We may also opt to perform arm-based NMA of safety outcomes.
- In meta-analysis, we will account for possible bias (and potentially also excess precision) in non-randomized evidence, for example using an approach suggested by Efthimiou et al. (16). To facilitate this, we may use existing meta-analytical software that supports multivariate and/or multi-level hierarchical network meta-regression (e.g., the metafor or nmaINLA R packages, versions 2.0-0 and 0.1.2 or later, respectively), or we may implement hierarchical Bayesian models using a tool such as JAGS or Stan.
- Where possible, and for each comparison, we will assess inconsistency between: direct randomized evidence; indirect randomized evidence; direct non-randomized evidence; indirect non-randomized evidence; network evidence from randomized evidence; and naïve network evidence (i.e., without accounting for potential differences between randomized and non-randomized evidence) as suggested by Efthimiou et al. (16). For example, we may judge there to be inconsistency if 95% confidence intervals or 95% credible intervals computed for these sources of evidence do not overlap.
- If we judge there is substantial inconsistency that is explained by the inclusion of evidence from particular non-randomized studies, we will omit those studies and report the omission. If we judge that inconsistency may be explained by potential treatment effect modifiers, we will attempt to include these as covariates in network meta-regression.

2. Removal of EQ-5D as an effect outcome

Health related quality of life as measured by the EQ-5D is used in the health economic evaluation in our HTA. However, the EQ-5D input data for this model does not come from the SR of RCTs, but from studies reporting the relationship between disability, as measured by the EDSS, and health related quality of life, as measured by the EQ-5D. Therefore, we will only retrieve EDSS, as a measure of disability progression, from the included studies.

3. Presenting absolute effect estimates

We originally planned to estimate relative measures of effect (e.g., annualized relapse rate ratios between pairs of treatments). To help readers understand our estimates of efficacy and safety, we now plan to also estimate and present absolute measures of effect (e.g., annualized relapse rates for each treatment).

Absolute effect measures can be calculated from relative effect measures if an absolute measure of effect can be estimated or assumed for a reference treatment, which is usually placebo. For example, if the relative measure of effect for serious adverse event (SAE) is an odds ratio (OR) between natalizumab and placebo, the absolute odds of SAE for natalizumab can be estimated by multiplying the estimated OR by the odds of SAE for placebo.

Where possible, we will estimate absolute measures of effect (to be used as reference values) for each outcome, using data from placebo arms published in studies that were included in the previous report but not eligible for inclusion in NMA performed for this project (i.e., we will obtain reference values from sources that are independent of those used in the NMA). We will estimate point estimates and 95% confidence intervals on these reference values using meta-analysis, and propagate uncertainty on the point estimates through to the confidence or credible intervals of the absolute effect estimates. We will report the reference values used when presenting the absolute effect estimates.

4. Legal and ethical aspects of off-label use of rituximab in Norway

An ethicist (Ingrid Miljeteig) and a legal advisor (TBD) have been appointed to assess the ethical and legal aspects of using an off-label drug for this indication. They are a part of the project group and will write their independent chapters, one for each topic. Information and perspectives should be given to them from the project group.

Ethical considerations

Elements in the ethical considerations will include, but are not restricted to:

a) Identification of the ethical aspects.
b) Description of the task and the process.
c) An ethical analysis of off-label use of rituximab in treatment of RRMS. In the analysis the potential outcome of various alternative solutions will be structured, relevant laws and regulations and involved stakeholders will be identified, potential burdens and benefits of the alternative solutions and the conflicts of interests will be revealed, as well as a throughout assessment of relevant values and principles at stake.

d) Discussion of what is most important to emphasize, potential value trade-offs, and possible ethically acceptable solutions.

Legal assessment

With respect to off-label use of medicines (i.e., rituximab), the legal consultant has been asked to outline and discuss the legal framework in Norway and the EU. The legal chapter will present a general statement of the legal background and a discussion of the specific use of the off-label drug rituximab and compare with similar situations if relevant.

5. User involvement

In the present report, a user is defined as a patient, a person from a relevant patient organisation or a caregiver.
At least two users will be asked to contribute to the report. At least one of the users should be a patient. We will ask the users to contribute through dialog between user and researcher. The users can give feedback to the assessment. It is however important to stress that it is not possible for the users to change the evidence based conclusions of the project. In particular, we need the users' views on which patient group, types of drugs, types of outcomes, as well as other concerns they find important in such a report.

6. Other changes

The original project plan incorrectly stated that mortality would be analysed as an annualized rate ratio. We will analyse mortality as a relative risk or odds ratio.

For non-randomised studies we used a checklist for cohort studies from the Handbook of Norwegian Institute of Public health (17) and not the ROBINS-I tool.

References

1. Compston A, Coles A. Multiple sclerosis. Lancet 2008;372(9648):1502-17. doi: 10.016/S0140-6736(08)61620-7.
2. Simpson S, Jr., Blizzard L, Otahal P, Van der Mei I, Taylor B. Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. J Neurol Neurosurg Psychiatry 2011;82(10):1132-41. doi: 10.6/jnnp.2011.240432. Epub 2011 Apr 8.
3. Berg-Hansen P, Moen SM, Harbo HF, Celius EG. High prevalence and no latitude gradient of multiple sclerosis in Norway. Mult Scler 2014;20(13):1780-2. doi: 10.177/1352458514525871. Epub 2014 Mar 6.
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.
5. What is a Serious Adverse Event?: FDA [cited]. Available from: https://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm
6. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: Cochrane Collaboration; 2011.
7. Rucker G. Network meta-analysis, electrical networks and graph theory. Research synthesis methods 2012;3(4):312-24.

8. Schwarzer G, Carpenter J, G R. Meta-Analysis with R (Use-R!): Sprinter International Publishing; 2015.
9. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE Decision Support Unit Technical Support Documents. In: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. London: National Institute for Health and Care Excellence (NICE) unless otherwise stated. All rights reserved.; 2014.
10. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Medical decision making : an international journal of the Society for Medical Decision Making 2013;33(5):607-17.
11. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Annals of internal medicine 2015;162(11):777-84.
12. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Statistics in medicine 2010;29(7-8):932-44.
13. Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC medical research methodology 2015;15:58.
14. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. Journal of clinical epidemiology 2011;64(2):163-71.
15. 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.
16. Efthimiou O, Mavridis D, Debray TP, Samara M, Belger M, Siontis GC, et al. Combining randomized and non-randomized evidence in network meta-analysis. Stat Med 2017;36(8):1210-26.
17. Folkehelseinstituttet. Slik oppsummerer vi forskning. Håndbok. 2014. Available from: https://www.fhi.no/kk/oppsummert-forskning-for-helsetjenesten/slik-oppsummerer-vi-forskning/