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Rituximab to Treat Primary Membranous Nephropathy — Project Protocol

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Abbreviations

ACTH	adrenocorticotropic hormone
AE	adverse event
eGFR	Estimated Glomerular Filtration Rate
ESRD	end-stage renal disease
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
ITC	indirect treatment comparison
KDIGO	Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines for Glomerulonephritis
MCMC	Markov Chain Monte Carlo
(P)MN	(primary) membranous nephropathy
NMA	network Meta-Analysis
NS	nephrotic syndrome
PICOS	Population(s), Intervention(s), Comparator(s), Study Design(s)
PLA2R	phospholipase A2 receptor
PO	project owner
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life-years
RCT	randomized controlled trial
RIS	Research Information Services
ROB	risk of bias
SAP	statistical analysis plan
SCr	serum creatinine
trt	treatment

Introduction and Rationale

Membranous nephropathy (MN) is an autoimmune disease and one of the most common causes of nephrotic syndrome (NS) in Caucasian adults.[1,2] NS is characterized by proteinuria (> 3.5 g/24 hours), hypoalbuminemia (< 30 g/dL), hyperlipidemia, and peripheral edema. Patients are also at risk of thromboembolism.[3] NS may lead to end-stage renal disease (ESRD).[4]

The incidence of MN is 1.2/100,000 persons per year worldwide.[2] Approximately 80% of patients with MN have anti-phospholipase A2 receptor (anti-PLA2R) antibodies and are classified as primary (or idiopathic) MN; whereas 20% of patients have secondary MN due to a malignancy, an infection (e.g., hepatitis B or C), drugs (e.g., penicillamine, non-steroidal anti-inflammatory drugs), an autoimmune disease (e.g., systemic lupus erythematosus), or a non-identified autoantibody.[1,2]

Spontaneous remission of primary MN is seen in up to 30% of patients,[1,2,5] and 30% to 40% of patients will progress to ESRD.[1] The occurrence of remission is more common in patients with low antibody levels.[1,2] Those with high levels of antibodies have higher risks of relapses, lower responses to therapy, and longer time to remission.[1,2]

The Toronto Risk Score is a validated tool that can predict the risk of progression to ESRD in patients with primary MN.[1] Patients at low risk will have normal serum creatinine/creatinine clearance and proteinuria ≤ 4 g /24 hours during a six-month observation period. Medium risk patients will have normal and stable renal function and with proteinuria of 5 g/24 hours to 8 g/24 hours during a six-month observation period. Those at high risk will have persistent proteinuria > 8 g/24 hours.[1]

The treatment goal of patients with primary MN is to achieve proteinuria remission to prevent renal damage.[2] Treatments include supportive therapies for hypertension, hyperlipidemia, edema, and for preventing thromboembolism.[1,2] There is evidence to show that immunosuppressive therapy reduces proteinuria, all-cause mortality, and progression to ESRD. Alkylating drugs (cyclophosphamide or chlorambucil) and calcineurin inhibitors (cyclosporine or tacrolimus) are immunosuppressive therapies recommended to treat patients with primary MN as described in the guidelines *The Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines for Glomerulonephritis 2012* (KDIGO).[6]

The 2012 KDIGO recommends using the Ponticelli regimen as initial treatment: in the first month, IV methylprednisolone 1g is administered daily for three doses, then oral methylprednisolone (0.5 mg/kg per day) is administered for 27 days. In the second month, oral cyclophosphamide[1] (2 mg/kg per day) is administered for 30 days. Months three and five are a repeat of the treatment regimen administered in the first month. Months four and six repeats the treatment regimen of the second month.[6]

Alternatively, calcineurin inhibitors may be administered for six months in patients who are not candidates for cyclophosphamide. The recommended dosing administration for cyclosporine is 3.5 mg/kg to 5.0 mg/ kg per day given orally in two equally divided doses 12 hours apart, with prednisone 0.15 mg/kg per day, for six months. Alternatively, tacrolimus is administered at a dosage of 0.05 to 0.075 mg/kg per day given orally in two divided doses

[a] Initially the Ponticelli regimen consisted of oral chlorambucil 0.15 mg/kg to 0.2 mg/kg per day and methylprednisolone, but the preference now is to use cyclophosphamide and methylprednisolone.

12 hours apart, without prednisone, for six to 12 months. The guidelines make further recommendations in case of resistance to treatment, relapses, and for children.[6]

The use of these medications are associated with serious adverse events. Patients administered cyclophosphamide are at risk of malignancy, infertility, infection, bone marrow suppression, liver toxicity, and cardiovascular events.[1,2] Serious adverse events seen in patients on calcineurin inhibitors include hypertension and nephrotoxicity.[a]

Other treatments for which there is evidence of efficacy include adrenocorticotropic hormone (ACTH), azathioprine, mycophenolate mofetil, and rituximab.[1,2]

Rituximab is a monoclonal antibody directed against the CD20 receptor. It induces the depletion of CD20 positive B-cells. Its use in primary MN was first reported in a case series in 2002 and subsequently in three single arm trials and one RCT that compared rituximab with supportive therapies.[2]

Rituximab does not have Health Canada approval for the indication of primary MN, and as a such is used off-label. Recently, three phase III RCTs have been conducted to evaluate rituximab compared with other immunosuppressive treatments in primary MN; one RCT has published results and the other two RCTs are completed but not yet published.

In July 2019, the MENTOR study on remission of proteinuria in 130 patients with primary MN was published.[7] It compared IV rituximab (two infusions, 1 g each, administered 14 days apart; repeated at six months in case of partial response) or oral cyclosporine (starting at a dose of 3.5 mg/kg per day for 12 months). Results demonstrated that:

- Rituximab was noninferior to cyclosporine in inducing proteinuria remission
- Rituximab was superior to cyclosporine in maintaining proteinuria remission.[7]
- A critical appraisal of the MENTOR study is posted on the CADTH website.[8]

The STARMEN study (ClinicalTrials.gov Identifier NCT019551870) investigated the use of cyclical cyclophosphamide-corticosteroid combination treatment for six months (Ponticelli regimen) compared with sequential tacrolimus-rituximab. The initial dose of oral tacrolimus was 0.05 mg/kg per day, adjusted to achieve blood trough levels of 5 ng/mL to 7 ng/mL for six months. At the end of month six, the tacrolimus dosage was reduced by 25% per month, with a complete withdrawal at the end of month nine. Rituximab was administered as a single dose of 1 g IV given at day 180, before the onset of the tacrolimus dose reduction. The trial was conducted in 86 patients with primary MN.[9] The study completion date was in June 2019.

The RI-CYCLO study (ClinicalTrials.gov NCT NCT03018535) evaluated rituximab 1 g administered on days 1 and 15, compared with six months of cyclical cyclophosphamide-corticosteroid combination treatment (Ponticelli regimen) in 76 adults with a diagnosis of primary MN.[10] The study completion date was in December 2019.

Several meta-analyses of RCTs have been published evaluating immunosuppressive therapies in primary MN; two of which included rituximab.[11-21]

An economic evaluation published in 2018 evaluated the cost-effectiveness of rituximab compared with the Ponticelli regimen. The evaluation was conducted from the perspective of the UK National Health Service using 2015 prices and based on an RCT by Jha et al.[22] that compared the Ponticelli regimen to supportive care and on an observational study by Ruggenenti et al.,[23] which included 100 consecutive patients treated with rituximab and no

control group. The results of the economic evaluation showed that, at five-years post-treatment, rituximab was cheaper than the Ponticelli regimen but at a loss of 0.014 quality-adjusted life-years (QALYs), with an incremental cost-effectiveness ratio (ICER) of £95,494.[24]

Project Scope and Protocol Development

To inform the final scope of this Health Technology Assessment project, and following review with CADTH jurisdictional clients, a proposed project scope document was posted to the CADTH website for stakeholder feedback.

Objectives

CADTH will undertake a Health Technology Assessment to review the available evidence on the use of rituximab for primary MN with the perspective of trying to determine its effectiveness and cost-effectiveness relative to cyclophosphamide and the calcineurin inhibitors.

Deliverables

The following deliverables are planned:

- a science report, including a clinical evaluation and an economic evaluation.

Policy Questions

The following policy questions are being addressed with this project:

1. Is there evidence to support the use of rituximab in adults patients with primary membranous nephropathy? If so, what are the policy options for providing access to rituximab?

Research Questions

The project will address the following research questions. Details on the specific interventions and outcomes are included in Table 1 — Selection Criteria.

1. What is the efficacy and safety of rituximab compared with current treatments in patients with primary membranous nephropathy?
2. What is the cost-effectiveness of rituximab compared with current treatments in patients with primary membranous nephropathy?

Methods

Clinical Review

Literature Search Methods

The literature search for clinical studies will be performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist (https://www.cadth.ca/resources/finding-evidence/press). [25] The draft search strategy is presented in Appendix 1.

Published literature will be identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid, and PubMed. The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept is membranous nephropathy. Clinical trial registries will also be searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal.

Search filters will be applied to limit retrieval to randomized controlled trials (RCTs) or controlled clinical trials. Retrieval will not be limited by publication date, but will be limited to the English or French language. Conference abstracts will be excluded from the search results.

The initial search will be completed spring 2020. Regular alerts will update the database literature searches until the publication of the final report. The clinical trial registries search will be updated before the completion of the stakeholder feedback period. Studies meeting the selection criteria of the review and identified in the alerts before the completion of the stakeholder feedback period will be incorporated into the analysis of the final report. Any studies identified after the stakeholder feedback period are described in the discussion section, with a focus on comparing the results of these new studies with the results of the analysis conducted for this report.

Grey literature (literature that is not commercially published) will be identified by searching sources listed in relevant sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist (https://www.cadth.ca/grey-matters),[26] which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, systematic review repositories, patient-related groups, and professional associations. Google will be used to search for additional internet-based materials. These searches will be supplemented by reviewing bibliographies of key papers and through contacts with experts and industry, as appropriate. The grey literature search will be updated before the completion of the stakeholder feedback period. See Appendix 1 for more information on the grey literature search strategy.

Data Source

The primary source of data will be those in the public domain. All stakeholders will be given the option of identifying and providing additional data.

Eligibility Criteria

Study Selection

Two reviewers will independently screen titles and abstracts for relevance to the clinical research questions. Full texts of potentially relevant articles will be retrieved and independently assessed for possible inclusion based on the predetermined selection criteria (Table 1). The two reviewers will then compare their chosen included and excluded studies; disagreements will be discussed until consensus is reached. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses, or PRISMA, flowchart.

Drug regimens eligible for inclusion in the review are those that have been approved by Health Canada or are considered of clinical relevance based on expert advice or international clinical practice guidelines. Drug products that are of interest to this review are shown in Table 1.

Inclusion and Exclusion Criteria

Table 1: Selection Criteria

Population	Adults with biopsy-proven primary membranous nephropathy with nephrotic syndrome **Subgroups:** • Risk for disease progression (e.g., age, severity of albuminuria, and anti-PLA2R status) • Relapse • Resistance to disease/prior failure with immunosuppressants • Treatment history (treatment-naive or experienced)
Interventions and **Comparators**[a]	• Rituximab monotherapy or combination therapy (e.g., with calcineurin inhibitors) • Cyclophosphamide with corticosteroids • Calcineurin inhibitors (cyclosporine or tacrolimus) with or without corticosteroids • Placebo/no treatment
Outcomes	**Clinical effectiveness:** • Outcomes assessing clinical response: complete remission, partial remission, time to remission, relapse • Outcomes assessing kidney function: kidney failure with or without renal replacement/end-stage renal disease (dialysis, kidney transplantation), doubling of SCr, or 50% reduction in eGFR • Health-related quality of life **Safety:** • Adverse events, serious adverse events, withdrawal due to adverse events, death • Notable harms: infection, gastrointestinal complications, neutropenia, neurologic, and malignancy
Study Design	• Phase III randomized controlled trials

Scr = serum creatinine; eGFR = Estimated Glomerular Filtration Rate; PLA2R = Phospholipase A2 receptor.

[a] Best supportive care may be given on an as-needed basis with all treatment regimens, which can include angiotensin converting-enzyme inhibitors or angiotensin II receptor blockers (ARBs); a diet low in salt and protein; statins; chlorambucil; ACTH; azathioprine; mizoribine; and leflunomide.

Data Extraction and Critical Appraisal

Study and participant characteristic data will be extracted by one reviewer and verified by a second reviewer using a standardized data extraction form developed a priori, which will then be piloted and modified as necessary. Abstraction will cover the following items:

- study characteristics, inclusion and exclusion criteria, and definitions where required
- baseline patient characteristic
- interventions evaluated, including dose, duration, route of administration, and concurrent and previous relevant therapies
- type of analysis (intention-to-treat or safety population)
- clinical safety and efficacy/effectiveness outcomes.

Study-specific outcomes data will be extracted independently by two reviewers. Any disagreements will be resolved through discussion and consensus with a third reviewer, if necessary.

The original, primary publication for each unique study included will be used for data extraction, except where multiple publications for a single primary study are found. Multiple publications for a unique study (e.g., supplemental online appendices, companion publications of specific outcomes, or populations from the original study) will be handled by extracting the most recently adjudicated data for each outcome specified a priori.

Quality Assessment

Quality assessment of comparative randomized studies will be performed independently by two reviewers using the Cochrane Risk of Bias (ROB) tool.

Data Analysis and Synthesis

After the conclusion of data extraction, we will conduct a feasibility assessment for addressing the posed research questions that will include evaluating sources of methodological and clinical heterogeneity between the included studies. Study design, patients baseline characteristics, treatment characteristics, as well as outcomes definitions will be compared between studies. A qualitative assessment of feasibility will be determined through close collaboration between the reviewers, methodologists, and clinical experts working on the HTA.

When feasible, we will evaluate the efficacy and safety of rituximab versus other relevant comparators outlined in the Table 1 through an indirect treatment comparison (ITC) using a network meta-analysis (NMA). However, if data on any outcomes or subgroups listed in Table 1 is limited, meta-analysis of direct comparisons and descriptive comparisons will be provided.

All NMAs will be conducted under a Bayesian framework. The modelling approach will be suitably chosen for each outcome, that is binomial likelihood models for dichotomous outcomes and normal likelihood models for continuous data. Random-effects models will be used as the primary approach when feasible to account for anticipated clinical and methodological heterogeneity across studies. Fixed-effects models will be considered when the available network for a given outcome is insufficient for estimating a random-effects model. When possible, regardless of the primary analysis, both fixed-effect and random-effect models will be reported along with diagnostic information criterion. Vague priors will be used for all parameters in the model. Each NMA will be modelled in a Markov Chain Monte Carlo (MCMC) simulation using three chains and their convergence will be assessed by examining the history, trace, and Gelman-Rubin plots. A minimum of 10,000 burn-ins and 20,000 iterations will be preformed in the simulation. In addition, statistical heterogeneity can be assessed through comparing the residual deviance between the fixed- and random-effects model. An assessment of the consistency assumption will be conducted through an

inconsistency model. Additional sensitivity analysis will be conducted by excluding studies with a high ROB or studies with missing data related to a relevant outcome.

Economic Analysis

Economic Evaluation

A primary economic analysis to evaluate the cost-utility of rituximab monotherapy or combination therapy (e.g., calcineurin inhibitor) compared to cyclophosphamide with corticosteroids, tacrolimus with or without corticosteroids, cyclosporine with or without corticosteroids, and best supportive care alone or no treatment for the treatment of biopsy-proven PMN in adults with NS will be conducted.

Primary Economic Analysis

A de novo decision analytic model will be developed to assess the costs and health outcomes associated with interventions for the treatment of biopsy-proven PMN in adult patients who have NS and have not achieved spontaneous remission within six months of diagnosis. The interventions considered will align with those in the Clinical Review, should data be available, and will include rituximab monotherapy or combination therapy (e.g., calcineurin inhibitor), cyclophosphamide with corticosteroids, tacrolimus with or without corticosteroids, cyclosporine with or without corticosteroids, and best supportive care alone or no treatment (i.e., placebo) (Table 1).

The patient cohort will be described by specific risk factors and clinical characteristics that will be identified from the Clinical Review. Separate patient subgroups may be assessed based on feedback from clinical experts consulted for this project and the availability of subgroup data.

Additionally, if feasible, the optimal sequencing of therapies (i.e., first-line and second-line combinations of the above interventions of interest) will be assessed. The sequences of interest will be those recommended for use in Canadian clinical practice and informed by the clinical expert consult by CADTH.

Model Design

An economic model will be developed to describe the movement of patients between health states reflective of the typical clinical progression of PMN. During the course of the patients' lifetime, their PMN may improve or deteriorate, depending on the effectiveness of the treatment for PMN, which may impact the natural progression of disease toward ESRD. The model will be used to evaluate, for the identified patient population, the cost-effectiveness of rituximab compared to other interventions currently used in clinical practice (Table 1).

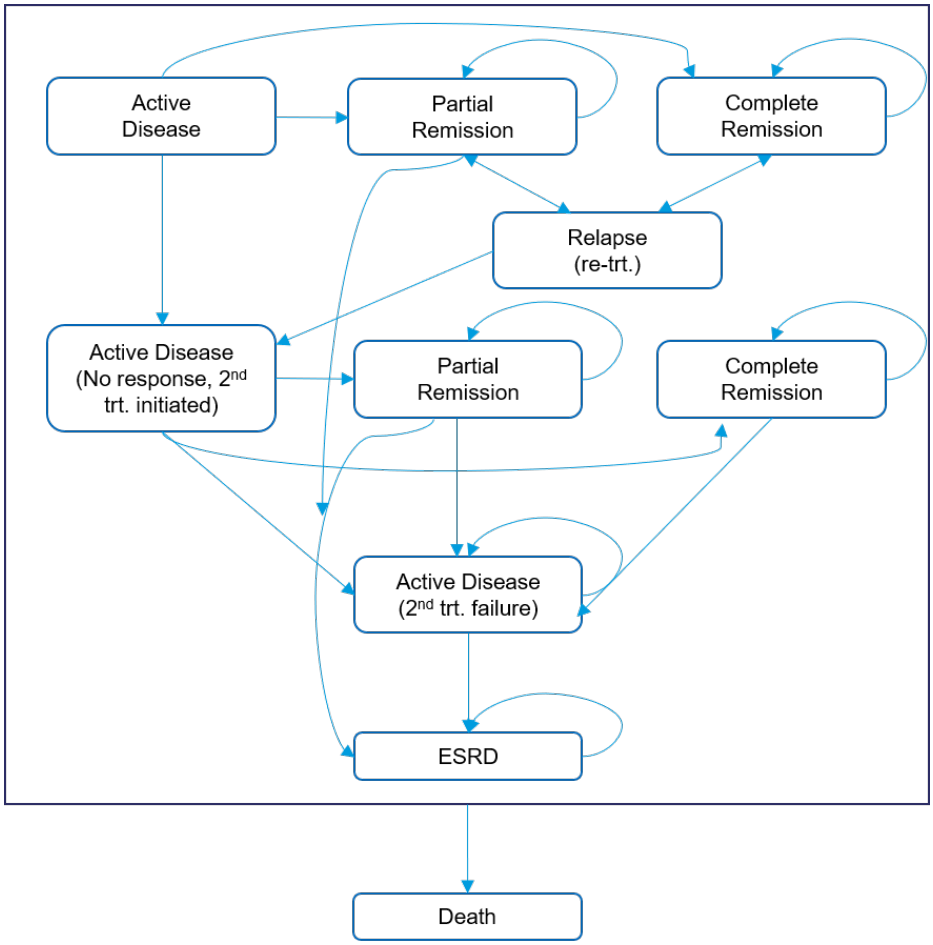
A cohort-level state transition (Markov) model will be developed that depicts health states relevant to the natural history of PMN and long-term effects of treatment. A draft model structure is presented in Figure 1. Health states would include active disease, partial remission (as defined by the Clinical Review), complete remission (as defined by the Clinical Review), relapse, as well as ESRD.

Patients would begin in the active disease health state and then have a probability of achieving complete remission, partial remission, or no response (and remain within active disease) according to their response to the intervention of interest based on the results of the Clinical Review. If the patient achieves partial or complete remission, then over time there is a

probability that the patient will relapse. If a patient does not achieve any form of remission, then they will continue to have active disease and receive a second line of therapy. If a patient experiences a relapse after achieving remission, they will be re-treated with the initial therapy, and if this fails, they will then also receive a second line of therapy. After receiving second-line therapy, the patient will either not respond or achieve partial or complete remission. If the patient does not respond to second-line therapy or relapses after achieving remission a second time, they will remain with active disease for the remainder of their life. At this stage the patient will be at risk of developing ESRD, that would encapsulate the typical treatments such as dialysis or renal transplant. Patients who are in either of the partial remission states will also be at risk of developing ESRD over time, at a reduced rate. The probability of dying throughout the model will be dependent on what state the patient is in.

The details of the model will be developed based on feedback from the CADTH Clinical Review team and the clinical experts to ensure that it reflects the current clinical literature and clinical practice. Both the internal and external validity of the model will be assessed for any logical discrepancies. The model will be constructed in Microsoft Excel.

Figure 1: Draft Model Structure



ESRD = end-stage renal disease; trt = treatment.

Perspective

The primary perspective in the model will be that of a publicly funded health care system (i.e., provincial ministry of health), focusing only on direct medical costs.

Resource Use and Cost Data

The costs captured in the model will reflect the scope of the project and the perspective of the economic analysis. Costs will include those related to the interventions, resource use related to patient health states, and event-related costs, as well as any additional relevant costs identified in consultation with clinical experts and the literature.

Canadian specific costs will be used, when available. If unavailable, costs will be estimated from the medical literature and, ideally, from comparable health systems. If necessary, costs will be adjusted to 2020 Canadian dollars, using the consumer price index.

Utilities

Utilities associated with each health state will be obtained from the literature from Canadian sources, where possible. The literature search of economic studies will provide the basis to identify suitable utility values and will be supplemented with additional literature searches as needed.

Clinical Parameters

Parameters describing the natural history of patients with PMN will be identified from peer-reviewed medical literature and medical registries to generate health state transition probabilities. In cases where no data are available to describe the natural history of PMN, a clinical expert will be consulted.

The Clinical Review will be primarily used to identify treatment effects describing the comparative clinical effectiveness of interventions for PMN. Additional information from the Clinical Review that is of interest to the economic model includes data on key safety parameters (e.g., infections, malignancies, nephrotoxicity, and infertility). In cases where no data are available to describe the impact of treatments to certain clinical outcomes, a clinical expert will be consulted.

Outcomes

The model will estimate the expected lifetime costs and QALYs for each of the included treatment strategies. The primary outcome will be the ICER, measured in terms of the incremental costs per QALY gained, of the treatment strategies on the efficiency frontier.

Costs, disaggregated by type, will also be reported. Additional outcomes, such as the reduction in serious adverse events of interest (e.g., infection, malignancy, and infertility), or complications with NS (e.g., thrombotic or thromboembolic events, and infection) may also be reported and will reflect the feedback received on clinically important outcomes from clinical experts.

Time Horizon and Discounting

A lifetime time horizon is proposed, with a maximum cohort age of 100, given that PMN is potentially life-long and that interventions to treat PMN may have different effects on both short- and long-term morbidity and mortality, resulting in differences in lifetime costs and

benefits. Discounting will be set at 1.5% per year as per CADTH Guidelines for the Economic Evaluation of Health Technologies: Canada.[27]

Sensitivity Analysis

The base-case analysis will represent the probabilistic findings, capturing the extent to which parameter uncertainty may impact the incremental cost-effectiveness findings. Results of the probabilistic analysis will be presented on a cost-effectiveness acceptability curve, whereby the probability each intervention is most likely cost-effective will be highlighted across different willingness-to-pay thresholds.

Probabilistic scenario analysis will be performed to evaluate key model assumptions and potential scenarios of interest, which may include:

- time horizon
- alternative efficacy inputs
- testing structural assumptions.

Uncertainty in the model will be further evaluated in a number of ways. Other analyses to address parameter uncertainty will include varying sets of related inputs (e.g., natural history inputs) or extreme scenarios (e.g., best- and worst-case analysis, threshold scenarios). This may help identify key inputs driving the results of the cost-effectiveness analysis.

Assumptions

During the course of the model development, assumptions and limitations will be identified and acknowledged in the report. Assumptions will be tested through the conduct of sensitivity analyses, where possible.

Opportunities for Stakeholder Feedback

Stakeholders have been previously given the opportunity to comment on the proposed project scope that informed this protocol. Stakeholders will be given the opportunity to provide feedback on the list of included studies, and the draft report.

Areas for Potential Amendments

If amendments are required at any time during the study, the reasons for changes will be recorded in a study file and subsequently reported within the final study report. If necessary, a rescreening of the previous literature search or an updated literature search will be performed to capture additional data according to the amendments.

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CADTH

Appendix 1: Literature Search Strategy

Draft Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) Cochrane Central Register of Controlled Trials (CCTR) **Note:** Subject headings will be customized for each database. Duplicates between databases will be removed in Ovid.
Date of Search:	To be determined
Alerts:	Monthly search updates will be run until project completion
Study Types:	Randomized controlled trials; controlled clinical trials
Limits:	Language limit: English and French-language Conference abstracts excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.dq	Candidate term word
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.jw	Journal word title
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

MULTI-DATABASE STRATEGY	
1	glomerulonephritis, membranous/ or Heymann Nephritis Antigenic Complex/
2	((extra?membranous or membranous) adj5 (nephropath* or Glomerulo* or nephritis)).ti,ab,kf.
3	((glomerular basement membrane* or glomerular membrane basement or GMB or GBM) adj5 thick*).ti,ab,kf.
4	((PMN or MGN) adj5 (nephropath* or kidney* or glomerul*)).ti,ab,kf.
5	(Heymann* adj2 Nephritis).ti,ab,kf.
6	1 or 2 or 3 or 4 or 5
7	6 use medall
8	membranous glomerulonephritis/ or Heymann nephritis/
9	((extra?membranous or membranous) adj5 (nephropath* or Glomerulo* or nephritis)).ti,ab,kw,dq.
10	((glomerular basement membrane* or glomerular membrane basement or GMB or GBM) adj5 thick*).ti,ab,kw,dq.
11	((PMN or MGN) adj5 (nephropath* or kidney* or glomerul*)).ti,ab,kw,dq.
12	(Heymann* adj2 Nephritis).ti,ab,kw,dq.
13	8 or 9 or 10 or 11 or 12
14	13 use oemezd
15	7 or 14
16	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
17	Randomized Controlled Trial/
18	exp Randomized Controlled Trials as Topic/
19	"Randomized Controlled Trial (topic)"/
20	Controlled Clinical Trial/
21	exp Controlled Clinical Trials as Topic/
22	"Controlled Clinical Trial (topic)"/
23	Randomization/
24	Random Allocation/
25	Double-Blind Method/
26	Double Blind Procedure/
27	Double-Blind Studies/
28	Single-Blind Method/
29	Single Blind Procedure/
30	Single-Blind Studies/
31	Placebos/
32	Placebo/
33	Control Groups/
34	Control Group/
35	(random* or sham or placebo*).ti,ab,hw,kf,kw.
36	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
37	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
38	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.
39	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.

MULTI-DATABASE STRATEGY	
40	allocated.ti,ab,hw.
41	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
42	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
43	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.
44	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.
45	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
46	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.
47	or/16-46
48	15 and 47
49	48 and (english or french).lg.
50	exp animals/
51	exp animal experimentation/ or exp animal experiment/
52	exp models animal/
53	nonhuman/
54	exp vertebrate/ or exp vertebrates/
55	or/50-54
56	exp humans/
57	exp human experimentation/ or exp human experiment/
58	or/56-57
59	55 not 58
60	49 not 59
61	glomerulonephritis, membranous/ or Heymann Nephritis Antigenic Complex/
62	((extra?membranous or membranous) adj5 (nephropath* or Glomerulo* or nephritis)).ti,ab,kw.
63	((glomerular basement membrane* or glomerular membrane basement or GMB or GBM) adj5 thick*).ti,ab,kw.
64	((PMN or MGN) adj5 (nephropath* or kidney* or glomerul*)).ti,ab,kw.
65	(Heymann* adj2 Nephritis).ti,ab,kw.
66	61 or 62 or 63 or 64 or 65
67	66 use cctr
68	60 or 67
69	68 not conference abstract.pt.
70	remove duplicates from 69

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period.	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period.	

Grey Literature

Search dates:	Spring 2020
Keywords:	Membranous nephropathy, glomerular basement membrane, GBM thickening, extramembranous nephropathy, Glomerular disease
Limits:	English and French-language only documents
Updated:	Search updated prior to the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) will be searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals.