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Rituximab versus the modified Ponticelli regime in the treatment of Primary Membranous Nephropathy: A health economic model

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Summary
Treatment for primary membranous nephropathy has remains still cyclophosphamide-based (the Ponticelli regimes), since the 1980s despite its high side-effect burden. Newer therapies such as Rituximab show promise but are expensive. We undertook a cost-effectiveness analysis of overall administration costings; based on UK NHS prices to compare Rituximab with than the modified Ponticelli regime, the current standard of care.
Background
Membranous Nephropathy is among the most common causes of nephrotic syndrome worldwide, with a high healthcare burden. Treatment using the modified Ponticelli regimes (mPR) has remained the standard of care for decades, but newer therapies such as Rituximab offer promising results with reduced side effects. The cost of this treatment however, is perceived as a barrier to widespread use; especially in resource limited healthcare systems.

Methods
We developed a decision-analytic model to estimate the cost-effectiveness of Rituximab versus the mPR from the perspective of the National Health Service in the UK over a one-year, five-year and lifetime horizon. Primary outcome is the cost-effectiveness of Rituximab vs. mPR at five-years post-treatment. Secondary outcomes are cost-effectiveness at 1 and 10 years post-treatment and over a lifetime.

Results
At one-year post-treatment, Rituximab therapy dominates mPR. At five-years post treatment, Rituximab therapy is cheaper than the Ponticelli regime but at a loss of 0.014 QALYs with an ICER of £95,494.13. Over a lifetime, Rituximab remains the cheaper option with an incremental cost of -£5251.03 but with a reduced quality of life (incremental QALY of -0.512) giving an ICER of £10,246.09.

Conclusions
Our analysis indicates that Rituximab has the potential to be a cost-effective treatment in the short and medium term despite the high single dose cost. This evaluation suggests that further research is warranted and highlights the need for a high quality clinical trial to confirm the efficacy and cost-effectiveness of Rituximab versus the current standard of care.
Introduction
Membranous nephropathy (MN) is one of the most common causes of adult nephrotic syndrome worldwide with a high healthcare burden in which approximately 20% of patients progress to end stage renal disease (ESRD)\(^1\)\(^2\).

MN has two distinct entities with primary MN (PMN) now considered to be an autoimmune disease since the discovery of the M-type of phospholipase A2 receptor 1 (anti-PLA\(_2\)R) antibodies\(^3\)\(^-\)\(^7\).

In PMN, disease activity and prognosis is still measured by proteinuria level and renal excretory function with the risk of renal decline falling in the presence of a reduction in proteinuria\(^6\)\(^-\)\(^{14}\). A key marker of treatment efficacy in PMN is therefore control of proteinuria, with or without immunosuppression\(^9\). Such immunosuppression is generally a combination of alkylating agents and steroids, as used in studies by Ponticelli et al\(^15\)\(^-\)\(^18\). This regime of rotating high dose intravenous steroids and immunosuppression was first described in 1984 and has been the mainstay of treatment since\(^{15}\). Initially using Methylprednisolone and Chlorambucil, it was later modified to include Methylprednisolone and Cyclophosphamide\(^15\)\(^-\)\(^18\). Despite its treatment success, the modified Ponticelli regime (mPR) bares a significant side effect profile, including an increased risk of infection, osteoporosis, diabetes mellitus, weight gain, haemorrhagic cystitis, infertility and malignancy\(^{16}\). This led many researchers to search for alternative therapies including tacrolimus and Mycophenolate Mofetil but with little evidence to show any improvement in outcomes\(^19\)\(^-\)\(^23\).

Rituximab has been used extensively in cancer therapy since the late 1990s and more recently for autoimmune diseases. A number of case series and studies have demonstrated potential in PMN but so far randomised controlled trials (RCT) have been scarce\(^24\)\(^-\)\(^28\). This, combined with the high cost of the medication itself, has restricted its widespread use in resource limited, evidence based, healthcare systems such as the National Health Service in the UK (NHS).

We developed a decision-analytic model to estimate the cost-effectiveness of Rituximab therapy versus the standard of care, namely the modified Ponticelli regime for the treatment of primary MN.
Methods
A cost-effectiveness analysis was carried out using a stochastic cohort Markov model developed using standard methods\textsuperscript{29}, conducted from the perspective of current practice in the UK NHS at 2015 prices.

The primary outcome was the cost-effectiveness of Rituximab versus mPR at five-years post treatment. Secondary outcomes were cost-effectiveness at one and ten years post-treatment and over a lifetime. A literature search revealed no studies directly comparing Rituximab versus mPR and therefore data was taken from the only studies of sufficient size to afford representative outcome assessment as described below. The analysis employed the cost-utility framework where the main measure of benefit is the quality-adjusted life year (QALY) and with analysis outcomes presented in terms of incremental cost-effectiveness ratios (ICER) of cost per QALY gained.

Choice of comparator
Here we have used the mPR which is the standard of treatment as per the KDIGO guidelines having established that the majority of UK renal centres use versions of the mPR as described by Ponticelli et al and Jha et al\textsuperscript{9,17,18,30}.

Model Structure
The model was developed in consultation with an expert panel including physicians, health economists and clinical scientists, and was identical for each treatment arm (see figure 1). For the treatment phase, all patients were assumed to experience active disease and costs were calculated from the papers described below. Following the treatment phase, patients could transition to (persistent) active disease, partial remission or complete remission. Health states then included sustained remission, relapse, ESRD (conservative management, haemodialysis or peritoneal dialysis and renal transplant) or death. Following the initial treatment phase, patients transitioned between health states on three-monthly cycles over a lifetime horizon. PMN is generally considered a disease of middle age with the median age of patients with PMN at diagnosis is 53 years old; we therefore extended the lifetime over an additional 47 years corresponding to a maximum survival of 100 years old\textsuperscript{31}.

Parameter values
Model parameter values and effectiveness of the interventions were based on the most robust data available for each arm; Jha et al for the mPR arm and Ruggenenti et al for the Rituximab arm\textsuperscript{18,26}. Jha et al was a prospective RCT comparing the mPR with supportive care, in biopsy proven adults (>16 years old) with nephrotic syndrome for more than 6 months duration and less than 2 months of treatment with either steroids or immunosuppression. There was a total of 93 patients completing the study, 47 receiving the mPR with oral cyclophosphamide and IV Methylprednisolone.

Ruggenenti et al published an observational study describing 100 consecutive patients, considered to be at a high risk of progressing to ESRD or to develop significant cardiovascular complications of their nephrotic syndrome, treated with Rituximab and no control group. It involved two distinct regimes; initially patients received Rituximab in four weekly doses of 375mg/m\textsuperscript{2}. However, as many patients on this regime were found to be B cell deplete after only the first dose of Rituximab, all subsequent patients from 2005 onwards were changed to a titrated regime. Prior to inclusion in the trial, 32 patients had received treatment with alternative immunosuppression. 20 of these did achieve partial remission prior to relapsing and necessitating treatment. The remaining 12 never achieved remission prior to starting Rituximab. Of the 100 patients described in the study, 71 received a single 375mg/m\textsuperscript{2} dose of Rituximab and only received a second dose if their serum B cells were more than 5 cells/mm\textsuperscript{3}. The cost of treatment in the Rituximab arm was therefore calculated using the same proportion of treatments (with corresponding outcomes) as in this study. This resulted in 29% of the total cost of treatment being taken as the cost of the initial four doses of 375mg/m\textsuperscript{2} Rituximab regime and 71% as the cost of the B-cell titration regime.

These papers were also chosen for their similar observational period allowing for a similar evaluation of care; however partial and complete remission were defined slightly differently (table 1), Jha et al having more stringent remission criteria. In practice, there is a cohort of patients that spontaneously remit but the majority will remain nephrotic and therefore require treatment. Both these studies, as in clinical practice, have included patients with biopsy proven membranous nephropathy and significant proteinuria warranting immunosuppression. Both studies have a male predominance reflecting clinical practice and the mean age at presentation was older in the study as described by Ruggenenti et al. Jha et al was carried out in India and Ruggenenti et al was carried out in Italy, two differing healthcare systems. However, both studies were carried out using standard methods and are comparable to use in the UK\textsuperscript{18,26}. See table 1.
Probabilities
Transition probabilities from the treatment phase to active disease, complete remission, partial remission, relapse and death were taken from the literature as above (Jha et al and Ruggenenti et al\textsuperscript{18,26}). Here there was an assumption of constant hazards based on survival at a single time point. If a patient developed ESRD they transitioned into the renal replacement pathway, which includes conservative management. Transition probabilities after ESRD have been obtained from the UK Renal Registry (2014)\textsuperscript{32}. Death rates were taken as those described in the study arms. At the end of the study follow up, UK Office of National Statistics (ONS) data was used to provide a baseline mortality rate\textsuperscript{33}. For patients in active disease, the death rate obtained from the ONS data was added to the transition probability from the studies. Once in partial or complete remission, death rate was taken as that in the ONS only. Death rates once in ESRD were taken from the UK Renal Registry.

Costs
Healthcare resource use included all healthcare contact, hospital stays, medication and serious adverse event (SAEs) episodes described in each publication. The cost of relapse was taken as the cost of treatment but without SAEs. Costs for each hospital/healthcare contact and SAEs were taken from the NHS reference costs 2014 to 2015\textsuperscript{34}. Standard Deviation estimated using $S = Q_3 - Q_1 / 1.35$\textsuperscript{35}. The cost of medication was taken from the Drugs and Pharmaceutical electronic market information (eMit) or from the British National Formulary 2015 if not available\textsuperscript{36,37}. For medications for which the dose is based on Body Surface Area we used $1.79m^2$\textsuperscript{38}. Maintenance therapy was not costed. Standard deviation of costs is not provided by the BNF so these were taken to be half the mean. (Table 2, 3 & 4). See supplementary material for table with disaggregated costs of treatment stage for reference case and regimes used in sensitivity analysis.

Utility/Quality of life
For many patients, the presenting symptoms that bring them to the notice of healthcare professionals, and ultimately to the diagnosis of PMN, is that of the nephrotic syndrome, namely oedema, increasing shortness of breath and fatigue. Currently there is limited data available on the quality of life (or utility) for patients with PMN, therefore utility values for
active disease were taken as that of active nephrotic syndrome, given these are the main
symptoms a patient will experience when their disease is active\textsuperscript{39}. For patients with partial or
complete remission we used age and sex matched EQ-5D UK population norms\textsuperscript{40}. Once
patients reached ESRD, utility values were estimated using SF-6D values from Wyld et al.
converted to utility scores\textsuperscript{41,42}. (Table 5).

Cost-effectiveness analysis
All costs are presented as mean cost per patient. Expected costs and QALYs were estimated
for each arm and, where appropriate, ICERs calculated (derived from the incremental cost of
treating with Rituximab and the incremental QALY). ICERs below the £20,000 threshold would
indicate that Rituximab is considered cost-effective as set by National Institute for Health and
Care Excellence (NICE) standards\textsuperscript{43}. Following NICE guidelines, half cycle correction was
conducted and a discount rate of 3.5\% per annum was applied to all outcomes incurred
beyond one year\textsuperscript{43}.

Incremental Net Monetary Benefit (INMB)
INMB’s were calculated using the incremental QALY, the incremental cost and the Lambda,
which in this case is £20,000, as per NICE guidelines\textsuperscript{43}. A positive value indicates that
Rituximab therapy is cost effective and therefore the preferred option when compared with
the mPR.

Deterministic Sensitivity Analysis
We performed one-way sensitivity analysis on a range of parameters to assess the impact of
each parameter on the outcome of the model at five-years post treatment as described by
the INMB. For sensitivity analysis of the costs, these were altered, the quality of life and
transition probabilities remaining unchanged. For sensitivity analysis of the transition
probabilities, the costs remained unchanged. Exact alterations to costs and probabilities are
given below.

\textit{Rituximab regimes}

The study described by Ruggenenti et al used to inform the Rituximab arm in our model
utilised two different regimes as described in the methods section. We therefore carried out
a sensitivity analysis based on all patients in the Rituximab arm receiving the original regime
consisting of four weekly infusions of 375mg/m\textsuperscript{2} Rituximab. We then carried out the analysis
based on all patients in the Rituximab arm receiving the B cell titrated regime ie a single 375mg/m$^2$ dose of Rituximab with a second dose if their serum B cells were subsequently more than 5 cells/mm$^3$. For both of these, the costs in the Ponticelli arm remained unchanged. Further sensitivity analysis was carried out using the recently reported RCT described by Dahan et al$^{27}$. Here patients in the treatment arm were given 2 doses of 375mg/m$^2$ Rituximab on days 1 and 8. For this analysis, only the costs in Rituximab arm of the model were changed and all outcomes remained the same.

**Ponticelli regimes**
The mPR uses low cost medications but requires multiple hospital admissions to receive steroid infusions. Therefore, to assess the impact that drug delivery has on the overall cost we performed a sensitivity analysis with patients only receiving oral prednisolone and no IV Methylprednisolone, with cyclophosphamide remaining unchanged. We also assessed how a change in the cyclophosphamide regime may affect the overall cost by carrying out a sensitivity analysis using pulsed monthly cyclophosphamide for 6 months with adjunctive oral prednisolone (with no IV methylprednisolone) as described by Kanigicherla et al$^{44}$. The costs for the Rituximab arm remained unchanged for both of these analyses.

**Other**
To assess how the cost of drug delivery itself affects the model outcomes we performed a sensitivity analysis with an increase and decrease in the cost of the delivery of an infusion in a day-care setting by 20% and on the cost of the medication itself (Rituximab and Cyclophosphamide). For the cost of infusion delivery, the cost was altered in both arms. For the cost of medication, the cost was altered in each arm and analysed separately.

In order to provide consistency, the cost of cancer in the original analysis was taken as the cost for the least severe form of the disease as per the NHS reference costs$^{34}$. To assess whether the cost of cancer impacts on the results we used the cost for the most severe form of the various cancers as reported in the NHS reference costs$^{34}$ for the sensitivity analysis. Given the known uncertainty in the quality of life measures available we performed a sensitivity analysis on this by altering the utility value of partial remission to be the same as active disease instead of complete remission. This was changed in both arms simultaneously.

**Transition probabilities**
To investigate the impact of the transition probabilities on outcomes, we performed a number of analysis including altering the death rate to be equal in both arms, the chance of developing ESRD and needing RRT to be equal in both arms and the rate of relapse to be equal in both arms. We analysed the effect of treatment efficacy by altering the transition probabilities of going from the treatment phase to either active disease, partial remission or complete remission by making them equal in both arms. We then altered the chance of transitioning from active disease to remission so that it was equal in both arms. We altered all transition probabilities to be equal in both arms with no change to costs or utility values. We also increased and decreased the probability, by 20%, of going into remission in the Rituximab arm and keeping the Ponticelli arm unchanged. We then performed the same analysis by altering the transition probability in the Ponticelli arm and kept the Rituximab arm unchanged.

Probabilistic Sensitivity Analysis
A probabilistic sensitivity analysis (PSA) was conducted with 10,000 Monte Carlo simulations based on random draws of all parameter values simultaneously from probability distributions. This provided 10,000 estimates of costs and QALYs, which were used to generate 10,000 ICERs and incremental net monetary benefit (INMB) estimates and allowed us to estimate the level of parameter uncertainty in the analysis. These simulated analyses were plotted on a cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC). The CEAC indicates the probability that Rituximab is cost-effective versus mPR across a range of willingness to pay per QALY gain thresholds. The higher the probability, the lower the uncertainty is in the model and decision.

Validation
We employed a number of tests to ensure the model was valid as possible although given the nature of the disease and lack of clinical trials, we were unable to perform a full validation. Validation was carried out using recognised techniques. Face validation was carried out with each aspect of the model design, data sources, formulae and eventual results reviewed and discussed by a panel of experts including clinicians, clinical scientists and health economists. Internal validation was performed using deterministic sensitivity analysis and testing whether changes in model inputs led to changes in outputs in the expected direction - for example by increasing the SAE / AE risks for Rituximab we expected the cost-effectiveness of that intervention would be reduced. Verification of the code was performed by one clinician and two separate and independent health economists.
As there are no other health economic or epidemiological models or RCTs in this area, cross validation, external validation and predictive validation were not possible.
Results
Incremental Cost-Effectiveness Ratio

At five-years post treatment, Rituximab therapy is cheaper than the Ponticelli regime but at a loss of 0.014 QALYs. Here the ICER is £95,494.13 (incremental cost -£1,355.82 and incremental QALY -0.014). At one-year post-treatment, Rituximab therapy dominates mPR. At 10 years post-treatment, Rituximab remains the cheaper option with an incremental cost of -£2,201.37. With an incremental QALY of -0.091 the ICER is £24,256.91. Over a lifetime the ICER was £10,246.09, obtained from the incremental per-patient cost of -£5,251.03 and incremental QALY of -0.512. See supplementary material for frequency of patients in each disease state at five-years post-treatment with corresponding costs and QALYs. See table 6.

Figure 2 - cost-effectiveness plane showing incremental costs versus incremental QALY at one-year, five-year and over a lifetime. Threshold line at £20,000 per QALY for 10,000 PSA simulations. At one-year and five-year post treatment the majority of simulated ICERs are in the right-hand side of the plane indicating Rituximab is more effective. There is a majority of patients in the lower half of the plane indicating that at five-years post treatment, Rituximab therapy is cheaper. The vast majority are below the £20,000 per QALY threshold set by NICE as the acceptable limit for the cost-effectiveness. Over a lifetime the majority of patients are in the left lower quadrant showing that Rituximab therapy is cheaper but less effective.

Cost

At five-years post treatment the cost for the mPR was -£13,116.65 and the cost for the Rituximab regime was £11,760.83, showing that the mPR is more expensive than Rituximab with an incremental cost of -£1,355.82. At one-year post-treatment, the cost of mPR and Rituximab was £8,676.10 and £7,927.90 respectively giving and incremental cost of -£748.20. At ten-years post-treatment, the cost of mPR was £17,834.30 and for Rituximab was £15,632.93, indicating that Rituximab continues to be cheaper with an incremental cost of -£2,201.37. Over a lifetime the cost of mPR is £29,943.80 compared to £24,692.77 for the mPR; an incremental cost of -£5,251.03. See table 6.

QALY

The QALY gains for mPR and Rituximab were 3.712 and 3.697 respectively at five-years post treatment, 0.952 and 0.954 respectively at one-year, 6.603 and 6.513 respectively at ten-years, and 14.162 and 13.650 respectively over a lifetime. Therefore, at one year Rituximab
confers QALY benefits over mPR but this is reversed by five-years and continues over a lifetime.

Incremental Net Monetary Benefit
At one-year, five-year and ten-year post treatment the incremental net monetary benefit (INMB) of Rituximab therapy is £785.44, £1,071.86 and £386.32 respectively, indicating Rituximab is more cost-effective. Over a lifetime the INMB is -£4,998.79 showing mPR is the more cost-effective option. See table 6.

Deterministic Sensitivity Analysis
Constrained to address outcomes with a mixed-protocol Rituximab analysis the sensitivity analysis confirms that a major driver of cost for Rituximab was the number of infusions required. The original four-dose regime is too expensive at five-years post treatment but for the B cell titrating regime and the regime described by Dahan et al27, at five-years post treatment, Rituximab is the cost-effective option. The other major drivers of cost-effectiveness in the Rituximab arm were death rate and the probability of reaching remission. For the mPR arm the main driver of the cost appears to be the frequency of infusions with removal of the cost of IV methylprednisolone resulting in the mPR being more cost-effective at five-years post treatment. The use of pulsed monthly IV cyclophosphamide alongside daily oral Prednisolone (again without IV Methylprednisolone) also resulted in the mPR being the most cost-effective at five-years post treatment. See figure 3 for full tornado plot of sensitivity analysis.

Cost effectiveness acceptability curve
Figure 4 - CEAC for the comparison based on the 10,000 PSA simulations. It shows the likelihood that Rituximab is cost-effective compared to mPR over a range of willingness-to-pay (WTP) per QALY gain threshold values (Lambda). At a lambda of £20,000 Rituximab has a 64% chance of being the cost-effective option at five-years post treatment. At a threshold of £30,000 this falls to 61%. This reflects the fact that Rituximab is the cheaper option at this time point but with a slightly reduced QALY.

Threshold analysis
In order for Rituximab to be the most cost-effective option over a lifetime, threshold analysis shows that the transition probability for treatment to active disease, partial remission and complete remission would have to change from 0.51250 to 0.61706, from 0.28500 to 0.22387 and from 0.20250 to 0.15907 respectively. Alternatively, the transition probability for active disease to death and partial remission to death for Rituximab would have to change from 0.00315 to 0.00136 and from 0.00680 to 0.00225 respectively.

Threshold analysis to determine the cost at which Rituximab represents the cost-effective option over a lifetime showed that due to the disparity in QoL there is no price at which it is cost-effective over a lifetime.
Discussion
The NHS, as with healthcare systems around the world, endeavours to provide the best care possible, with limited resources, for its aging population and increasingly complex patients. This has resulted in NICE, the regulatory body, considering not only the health benefits of therapies but also their economic impact.

Rituximab has become increasingly important in the treatment of a range of autoimmune conditions\textsuperscript{48-58}. Its attraction lies in its more directed immunoregulation and reduced side effect profile as compared to other immunosuppressants. Its single dose cost however, has limited its use in conditions such as MN, especially where there is a paucity of evidence from RCTs available.

With this lack of RCTs but with good evidence that Rituximab can provide a benefit for patients in a number of trials and case series\textsuperscript{24-28}, we constructed a Markov model to assess its cost-effectiveness when compared to the standard of care, i.e. the mPR. Using costs from the UK NHS we found that at every time point analysed Rituximab was the cheapest option and this was especially true if using the B-cell titration regime. At one year post-treatment, the QALY was better using Rituximab than the mPR, but over a life-time this reduced with the mPR providing an increment of approximately half a QALY. However, Rituximab may still represent value for money given the cost savings are so high for every QALY lost.

It appears that the main driver of cost for the mPR is the frequency of infusions, adding cost to an inexpensive medication such as Methylprednisolone. This is also true for Rituximab, with the original regime, in which patients have four doses, proving less cost-effective\textsuperscript{25}. In the B-cell titration regime\textsuperscript{24}, patients continue to have a good response to treatment but with fewer infusions making it consistently more cost-effective.

The reduction in quality of life for Rituximab over time is in part associated with the slightly increased risk of death and to a lesser extent the higher risk of relapse after Rituximab. Our model, however, is a conservative estimate for the quality of life benefits from Rituximab, as we do not take into account late complications associated with the therapies. It is well documented that there is an increased risk of malignancy many years after treatment with Cyclophosphamide\textsuperscript{59}. Rituximab in contrast, appears to have fewer complications and no indication of an increased risk of malignancy. Our model does not capture the quality of life associated with the provision of treatment, such as early onset side effects, notably nausea in cyclophosphamide, or with the number of visits. With the reduced side effect profile and reduced hospital visits needed for Rituximab therapy one could deduce that this would contribute to an improved quality of life although this is not possible to prove in this model.
This is the most comprehensive estimate of the cost-effectiveness of treatment for PMN to date but it does come with limitations. The spread of results on the scatterplot for the PSA at the lifetime horizon indicates significant uncertainty in the results with the robustness of data available degenerating over time. This highlights the need for further good quality long-term prospective research comparing these therapies. Another limitation is that this evaluation was based on a naive comparison, if other single arm or cohort study data becomes available it may be that an indirect comparison would then be feasible.

Due to the paucity of RCTs investigating the efficacy of Rituximab in PMN we opted to base the Rituximab arm on the largest data series available for its use in this condition. This is a prospective observational study with all the limitations this confers on the data such as patient selection and centre bias but it remains the most robust data available.

This and the Jha study used to inform the model are international studies (Italy and India) but for precision our model is costed to the UK health system. At present, there are no large-scale clinical trials published using Rituximab in a UK population, and there have been no large clinical trials in the UK using Cyclophosphamide for the treatment of PMN.

Another limitation has been the assignment of utility values to the disease. There is good validated data for population norms but renal specific quality of life data is scarce. This meant for active disease and RRT we had to convert SF-36 scores to utility values using standard methods\textsuperscript{39-42}.

PMN can be a slowly progressing disease with many patients following a relapsing and remitting pattern over a number of years. Here we used only the rates for transition to ESRD and RRT as described in the two papers. This is likely to have underestimated the degree to which patients progressed to ESRD over a lifetime due to the relatively short follow up time of the studies. Given the uncertainty already apparent in the model over a lifetime, it adds further evidence for the need for long term RCTs in PMN.

This model has only included the cost of therapy at a tertiary level. It was beyond the scope of the study to assess the overall societal cost and there is likely to be significant cost to patients, families and carers in the form of lost days of work, travel costs, equipment costs. The cost of primary healthcare contact has also not been included in this model.

Conclusion
Rituximab has shown promise as a therapy for PMN in a number of studies but the high cost of the medication has proven to be a barrier to its widespread acceptance. Here we have constructed the most detailed economic model yet for the treatment of PMN and show that Rituximab is not more expensive than the gold standard treatment and is cheaper over a lifetime. This work highlights the uncertainty surrounding PMN treatment with the small number of RCTs available to guide practitioners and commissioning bodies. Based on the evidence available, the longer-term effectiveness of Rituximab in PMN needs further evaluation, and importantly, long-term trials comparing Rituximab with cyclophosphamide-based therapy should be undertaken to help establish the most cost-effective management of the condition.

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Figure 1

Figure 2

- PSA over a lifetime
- PSA at 10 years post treatment
- PSA at 5 years post treatment
- PSA at 1 year post treatment
- Linear (£20,000 per QALY)
### Table 1

<table>
<thead>
<tr>
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<th>Jha et al.</th>
<th>Ruggenenti et al.</th>
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<td><strong>Cohort size</strong></td>
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<td><strong>or</strong> Proteinuria ≥ 2.5g/d &amp; serum albumin &lt; 2.5g/dl with oedema and hyperlipidaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Partial remission</strong></td>
<td>Proteinuria &lt; 2.0g/d or ≥ 50% reduction from baseline</td>
<td>Proteinuria &lt; 3.0g/d &amp; ≥ 50% reduction from baseline</td>
</tr>
<tr>
<td><strong>Complete remission</strong></td>
<td>Proteinuria &lt; 0.3g/d</td>
<td>Proteinuria &lt; 0.3g/d &amp; ≥ 50% reduction from baseline</td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td>Not defined</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events – n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>During Infusion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergy</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bronchial wheezing</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cutaneous rash</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>TIA</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Acute MI</td>
<td>1 (1)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Cancer</td>
<td>0 (0)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>3 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Disseminated tuberculosis</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>3 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (1)</td>
<td>4 (4)</td>
</tr>
</tbody>
</table>

**Table 1 – Comparison of trials used for model**

### Table 2

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Pack size</th>
<th>Treatment Dose</th>
<th>Mean Value ($)</th>
<th>SD ($)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Methylprednisolone</td>
<td>1000mg</td>
<td>1 pack</td>
<td>1000mg</td>
<td>11.04</td>
<td>5.90</td>
<td>eMIT</td>
</tr>
<tr>
<td>Prednisolone tablets</td>
<td>5mg</td>
<td>100 tablets</td>
<td>35mg</td>
<td>4.39</td>
<td>0.26</td>
<td>eMIT</td>
</tr>
<tr>
<td>PO Cyclophosphamide</td>
<td>50mg</td>
<td>300</td>
<td>140mg</td>
<td>82.00</td>
<td>41.00</td>
<td>BNF</td>
</tr>
<tr>
<td>IV Cyclophosphamide</td>
<td>1000mg</td>
<td>1 vial</td>
<td>375mg/m²</td>
<td>174.63</td>
<td>87.32</td>
<td>eMIT</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>10mg/ml</td>
<td>10 mL vial</td>
<td>100mg</td>
<td>873.15</td>
<td>436.58</td>
<td>BNF</td>
</tr>
<tr>
<td>Basilixim</td>
<td>20mg</td>
<td>1 vial</td>
<td>842.38</td>
<td>421.39</td>
<td>BNF</td>
<td></td>
</tr>
<tr>
<td>IV Hydrocortisone</td>
<td>100mg/mL</td>
<td>1 mL amp</td>
<td>100mg</td>
<td>1.08</td>
<td>0.54</td>
<td>BNF</td>
</tr>
<tr>
<td>Maropitantol</td>
<td>100mg</td>
<td>10 mL amp</td>
<td>1000mg</td>
<td>0.52</td>
<td>0.29</td>
<td>eMIT</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>8mg</td>
<td>8 mg</td>
<td>8 mg</td>
<td>1.06</td>
<td>0.58</td>
<td>eMIT</td>
</tr>
<tr>
<td>IV Chlorphosphamine</td>
<td>10mg/1ml</td>
<td>5 ampoules</td>
<td>10mg</td>
<td>22.80</td>
<td>3.52</td>
<td>eMIT</td>
</tr>
<tr>
<td>PO Mesna</td>
<td>400mg</td>
<td>10 tablets</td>
<td>200mg</td>
<td>42.90</td>
<td>21.45</td>
<td>BNF</td>
</tr>
<tr>
<td>IV Mesna</td>
<td>160mg/mL</td>
<td>4 mL vial</td>
<td>200mg</td>
<td>3.55</td>
<td>1.96</td>
<td>BNF</td>
</tr>
<tr>
<td>Normal Saline</td>
<td>1000ml</td>
<td>1 bag</td>
<td>1000ml</td>
<td>0.80</td>
<td>0.40</td>
<td>BNF</td>
</tr>
</tbody>
</table>

**Table 2 – Cost of medication. All medications oral unless otherwise stated. All doses based on weight of 70kg patient. All prices based on dose and pack size. SD – Standard deviation. eMIT – Department of Health electronic market information tool accessed on 30th June 2016 and costs correct to December 2015 onwards. Prices given in eMIT are excluding VAT therefore taken as 20%. BNF – British National Formulary accessed on 30th April 2015 onwards. Standard Deviations for BNF meds taken as Mean / 2 as they are not provided.**
### Table 3

<table>
<thead>
<tr>
<th>Health Service</th>
<th>Mean Value</th>
<th>LQR</th>
<th>UQR</th>
<th>SD</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery of Chemo (11)</td>
<td>257.00</td>
<td>136.00</td>
<td>311.00</td>
<td>129.63</td>
<td>SB122 NHS ref costs</td>
</tr>
<tr>
<td>Simple Parenteral</td>
<td>414.00</td>
<td>250.00</td>
<td>521.00</td>
<td>200.74</td>
<td>SB142 NHS ref costs</td>
</tr>
<tr>
<td>Complex &amp; Infusional</td>
<td>362.00</td>
<td>230.00</td>
<td>413.00</td>
<td>135.56</td>
<td>SB152 NHS ref costs</td>
</tr>
<tr>
<td>Subsequent chemo</td>
<td>1910.66</td>
<td>1334.41</td>
<td>2342.81</td>
<td>746.96</td>
<td>YCA2Z NHS ref costs</td>
</tr>
<tr>
<td>AVF, Graft or Shunt DC</td>
<td>1268.00</td>
<td>503.00</td>
<td>1815.00</td>
<td>971.85</td>
<td>LA052 NHS ref costs</td>
</tr>
<tr>
<td>PD associated procedure DC</td>
<td>160.00</td>
<td>110.00</td>
<td>185.00</td>
<td>55.56</td>
<td>WF01A 361 NHS ref costs</td>
</tr>
<tr>
<td>Nephrology clinic</td>
<td>358.00</td>
<td>220.00</td>
<td>493.00</td>
<td>202.22</td>
<td>WF01A 102 NHS ref costs</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>166.00</td>
<td>143.00</td>
<td>176.00</td>
<td>24.44</td>
<td>RENALCKD LD02A NHS ref costs</td>
</tr>
<tr>
<td>Peritoneal Dialysis</td>
<td>71.00</td>
<td>50.00</td>
<td>67.00</td>
<td>12.59</td>
<td>RENALCKD LD12A NHS ref costs</td>
</tr>
<tr>
<td>Renal Transplant</td>
<td>12,847.93</td>
<td>10,177.90</td>
<td>14,250.00</td>
<td>3015.56</td>
<td>LA01A NHS ref costs</td>
</tr>
<tr>
<td>Cadaver NHB</td>
<td>12,434.09</td>
<td>12,004.00</td>
<td>14,450.00</td>
<td>1145.19</td>
<td>LA02A NHS ref costs</td>
</tr>
<tr>
<td>Live donor</td>
<td>13,828.19</td>
<td>9990.00</td>
<td>17,750.00</td>
<td>3574.15</td>
<td>LA03A NHS ref costs</td>
</tr>
<tr>
<td>Pre-transplant work-up</td>
<td>1205.75</td>
<td>958.00</td>
<td>1599.00</td>
<td>445.19</td>
<td>LA11Z NHS ref costs</td>
</tr>
<tr>
<td>Live donor</td>
<td>5.00</td>
<td>2.00</td>
<td>7.00</td>
<td>3.70</td>
<td>DAPS06 NHS ref costs</td>
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</table>


### Table 4

<table>
<thead>
<tr>
<th>Complication</th>
<th>Mean</th>
<th>LQR</th>
<th>UQR</th>
<th>SD</th>
<th>Source</th>
<th>Notes/Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory tract infections</td>
<td>1540.00</td>
<td>1255.00</td>
<td>1685.00</td>
<td>218.52</td>
<td>D2220 NHS ref costs</td>
<td>Unspecified acute URTI (0-1)</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>1508.00</td>
<td>1288.00</td>
<td>1659.00</td>
<td>815.56</td>
<td>LA045 NHS ref costs</td>
<td>Kidney/UTI – no intervention (0-1)</td>
</tr>
<tr>
<td>Glucose Abscess</td>
<td>1535.00</td>
<td>906.00</td>
<td>1557.00</td>
<td>642.22</td>
<td>HD256 NHS ref costs</td>
<td>MRK signs or symptoms (0-3)</td>
</tr>
<tr>
<td>Bacterial Meningitis</td>
<td>1239.00</td>
<td>1561.00</td>
<td>2538.00</td>
<td>797.78</td>
<td>AA226 NHS ref costs</td>
<td>Nervous system infections (0-4)</td>
</tr>
<tr>
<td>Pulmonary Tuberculosis</td>
<td>1200.00</td>
<td>1702.00</td>
<td>3331.00</td>
<td>1068.52</td>
<td>DZ14 NHS ref costs</td>
<td>Pulmonary pleural, other Tb (0-1)</td>
</tr>
<tr>
<td>Septicemia</td>
<td>1593.00</td>
<td>1585.00</td>
<td>2224.00</td>
<td>472.59</td>
<td>W058 NHS ref costs</td>
<td>Sepsis (0-1)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1862.00</td>
<td>992.00</td>
<td>1491.00</td>
<td>869.63</td>
<td>YC018 NHS ref costs</td>
<td>DVT (0-2)</td>
</tr>
</tbody>
</table>

Ruggenenti et al

| Acute MI                           | 1505.00 | 1205.00 | 1701.00 | 367.41 | EB10E NHS ref costs        | Actual/Suspected MI (0-3)                              |
| Stroke                             | 2348.00 | 1803.00 | 2597.00 | 588.15 | AA35F NHS ref costs        | Stroke (0-3)                                           |
| TIA                                | 1253.00 | 978.00 | 1399.00 | 307.41 | AA226 NHS ref costs        | TIA (0-4)                                              |
| Lung cancer                        | 3047.00 | 2063.00 | 3610.00 | 1145.93 | D217R NHS ref costs       | Resp. neoplasms (0-5)                                  |
| Breast cancer                      | 3357.00 | 1504.00 | 4554.00 | 2398.28 | IA155 NHS ref costs       | Malignant – intervention (0-2)                         |
| Prostate Carcinoma                 | 2268.00 | 1498.00 | 2000.00 | 882.22 | LB00M NHS ref costs       | Prostate Ca – intervention (0-1)                       |

Table 4 – Cost of AEs and SAEs. All costs given in British Pounds. NHS ref costs – National Health Service reference costs 2014 – 2015[8]. LQR – Lower Quartile Range. UQR – Upper Quartile Range. CC Score in parenthesis. TIA – Transient Ischaemic Attack. All costs taken as non-effective cost stay. Standard Deviation estimated using SD = Q3 – Q1 / 1.35 from Cochrane Handbook from Systematic Reviews and Interventions 2008[9].
Table 5

<table>
<thead>
<tr>
<th>Utility</th>
<th>Mean</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>SD / SE</th>
<th>Source</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>0.860</td>
<td>0.630</td>
<td>1.000</td>
<td>0.230</td>
<td>Kind et al.</td>
<td>Age &amp; Sex matched</td>
</tr>
<tr>
<td>Partial remission</td>
<td>0.860</td>
<td>0.630</td>
<td>1.000</td>
<td>0.230</td>
<td>Kind et al.</td>
<td></td>
</tr>
<tr>
<td>Active disease</td>
<td>0.738</td>
<td>0.422</td>
<td>1.000</td>
<td>0.317</td>
<td>Liborio et al.</td>
<td>SF36 converted to EQ5D</td>
</tr>
<tr>
<td>ESRD</td>
<td>0.800</td>
<td>0.650</td>
<td>0.940</td>
<td>0.030</td>
<td>Wyld et al.</td>
<td>CKD (pre-treatment)</td>
</tr>
<tr>
<td>Conservative</td>
<td>0.620</td>
<td>0.360</td>
<td>0.890</td>
<td>0.090</td>
<td>Wyld et al.</td>
<td>SF36 converted to EQ5D</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>0.680</td>
<td>0.530</td>
<td>0.820</td>
<td>0.020</td>
<td>Wyld et al.</td>
<td>SF36 converted to EQ5D</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>0.710</td>
<td>0.590</td>
<td>0.820</td>
<td>0.020</td>
<td>Wyld et al.</td>
<td>SF36 converted to EQ5D</td>
</tr>
<tr>
<td>Renal transplant</td>
<td>0.820</td>
<td>0.740</td>
<td>0.900</td>
<td>0.040</td>
<td>Wyld et al.</td>
<td>SF36 converted to EQ5D</td>
</tr>
<tr>
<td>Dead</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5 – Quality of life utility values. ESRD – End-stage renal disease. Partial remission and Complete Remission taken as the same.

Table 6

<table>
<thead>
<tr>
<th></th>
<th>Deterministic Sensitivity Analysis</th>
<th>Probabilistic Sensitivity Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incremental Cost</td>
<td>Incremental QALY</td>
</tr>
<tr>
<td>One year</td>
<td>-£1,748.20</td>
<td>0.002</td>
</tr>
<tr>
<td>Five years</td>
<td>-£1,355.82</td>
<td>-0.014</td>
</tr>
<tr>
<td>Ten years</td>
<td>-£2,203.37</td>
<td>-0.091</td>
</tr>
<tr>
<td>Lifetime</td>
<td>-£5,261.00</td>
<td>-0.512</td>
</tr>
</tbody>
</table>

Table 6 – Results for both probabilistic and deterministic sensitivity analysis at one, five and ten years post treatment and over a lifetime. Lambda taken as £20,000. QALY – Quality-adjusted life year. ICER – Incremental cost-effectiveness ratio. INMB – Incremental net monetary benefit.
References


25. Remuzzi G, Chiurchiu C, Abbate M et al. Rituximab for idiopathic membranous


41. Ara R, Brazier J. Deriving an Algorithm to Convert the Eight Mean SF-36 Dimension Scores into a Mean EQ-5D Preference-Based Score from Published Studies (Where Patient Level Data Are Not Available). Value in Health. 2008 Dec;11(7):1131–43.


