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HOW TO HANDLE LEVELS OF EVIDENCE IN HEALTH ECONOMIC MODELLING

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OBJECTIVES: To address the practical and methodological issues associated with using low-quality evidence outcomes in health economic modelling. **METHODS:** A cost-effectiveness model for disease-modifying drugs (DMDs) in multiple sclerosis (MS) in The Netherlands was used to assess how to deal with low-quality evidence in health economic modelling. The model adopted a 10-year time horizon and a societal perspective. A Markov model was constructed based on EDSS staging in MS, including relapse. The central focus was on disease progression — instead of relapse — which appeared to be the driver of the cost-effectiveness outcomes. The main data source was a recent Cochrane review estimating relative efficacy and acceptability of DMDs in relapse-remitting MS. Other data sources included additional published literature, clinical trials, and official price/tariff lists. **RESULTS:** The analysis based on the Cochrane review data showed that interferon beta-1a-R (Rebif) is cost-effective over interferon beta-1a-A (Avonex) (dominant) and interferon beta-1b (€27,654/QALY), but that interferon beta-1a-R is not cost-effective over glatiramer acetate. However, for disease progression, the level of evidence is considered very low (level 1) for all drugs, except interferon beta-1a-R (moderate - level 3), implying unreliable effectiveness outcomes which, consequently, can result in unreliable cost-effectiveness outcomes. Two reasonable alternative approaches may be to exclude very low evidence from the cost-effectiveness analysis or assume placebo efficacy. Alternative analyses, including placebo efficacy for disease progression for drugs of which the evidence is labelled very low by Cochrane (all except interferon beta-1a-R), strongly impacted outcomes: interferon beta-1a-R was cost-effective over interferon beta-1a-A (dominant), interferon beta-1b (€6,265), and glatiramer acetate (dominant). **CONCLUSIONS:** Inclusion of very low-quality evidence in health economic modelling may lead to unreliable cost-effectiveness conclusions. However, a gold standard is lacking for handling levels of clinical evidence in health economic models. One alternative, presented here, would be to assume placebo efficacy in such cases.

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BEST PRACTICES FOR NETWORK META-ANALYSIS METHODOLOGY: COMPARATIVE EFFECTIVENESS OF INTERFERON-BETA THERAPIES IN RELAPSING-REMITTING MULTIPLE SCLEROSIS

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OBJECTIVES: To evaluate different statistical methodologies in a network meta-analysis (NMA) comparing the effectiveness of interferon-beta (IFNβ) therapies across several endpoints in relapsing-remitting multiple sclerosis (RRMS) to determine potential best practices. **METHODS:** A systematic literature review (1996-2014) was conducted to identify randomised, controlled trials of FDA- and EMA-approved IFNβ DMDs in RRMS, including subcutaneous (SC) IFNβ-1a (44µg or 22µg 3x/wk), SC pegIFNβ-1a (125µg every 2wks), intramuscular (IM) IFNβ-1a (30µg 1x/wk), and SC IFNβ-1b (250µg EOD). Data were extracted for patients relapse-free, patients without disability progression, and patients without new MRI activity at study end. A random-effects Bayesian model was utilised for the base case analysis, and sensitivity analyses investigated results using different analysis frameworks or effects distributions. **RESULTS:** 644 articles were retrieved; 14 met inclusion criteria and reported evaluable data. The evidence networks had few connections between nodes, with a maximum of 10 connections for the proportion of "patients relapse-free" endpoint. In addition, there were few connections with multiple studies linking nodes, with a maximum of 50% (5/10) of connections having more than one study on the relapse endpoint, and there were at most two studies linking any two nodes. Because of the small number of studies linking nodes, a random-effects Bayesian model with uninformative priors resulted in wide credible intervals, complicating interpretation of results; uncertainty decreased using a random-effects Bayesian model with an informative prior as well as with a fixed-effects Bayesian model. Estimates for the treatment effects were similar across all Bayesian approaches. Utilising a Frequentist approach resulted in similar estimates for treatment effects compared to the Bayesian analyses framework, although with slightly less uncertainty. **CONCLUSIONS:** While similar estimates for treatment effects were found across statistical methodologies, the combination of a Bayesian approach and a random-effects distribution with informative prior allowed for methodological robustness while yielding interpretable findings.

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REVIEW OF ECONOMIC MODELS FOR THE EVALUATION OF BIOLOGIC DMARDS IN RHEUMATOID ARTHRITIS

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OBJECTIVES: Over the last decade, several biologic disease-modifying anti-rheumatic drugs (bDMARDs) have become available providing additional treatment options for rheumatoid arthritis (RA) patients. This study was conducted to identify and compare existing economic models used by health technology assessment (HTA) bodies to evaluate bDMARDs. **METHODS:** The HTA Accelerator database and websites of HTA agencies (NICE, SMC, NCPE, ZIN, TLV, PBAC, CADTH, INESSS, MOHLTC, DECIT-CGATS and AHRQ) were screened to identify assessments of bDMARDs published since 2005 that included a cost-utility analysis (CUA). In addition, a targeted literature review was performed to gain further insights on model constructs, key data elements/assumptions, and recent modeling advances. **RESULTS:** Thirty-three HTAs comprising 60 CUAs were considered relevant and investigated further. Albeit individual sampling models and discrete event simulations have some advantages over Markov models, these three techniques may provide similar cost-effectiveness estimates and were all deemed appropriate for HTA submissions. At least ten different structural components were identified for which data sources and/or assumptions have evolved over time, several of which have a major bearing on model outcomes. The characteristics of patients entering the model (e.g. disease severity and prior treatments), assumptions about long-term disease progression whilst on treatment and the rebound effect upon treatment discontinuation, and mapping of Health Assessment Questionnaire and/or pain scores to Quality of Life utility values were repeatedly mentioned as key elements affecting the results. **CONCLUSIONS:** A wide variety of economic models for the evaluation of bDMARDS in RA have been developed and are continuously being refined. Despite recent initiatives to reach consensus on how RA models should be designed, substantial differences in the data sources and assumptions that are used still remain. This limits the comparability across and also generalizability of the various results obtained by using these models and poses problems to all stakeholders involved in HTAs.

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INVESTIGATING THE IMPACT OF STRUCTURAL CHANGES IN A NICE SINGLE TECHNOLOGY APPRAISAL COST-EFFECTIVENESS MODEL

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OBJECTIVES: One of the major critiques with submitted manufacturer's cost-effectiveness models is surrounding the structural uncertainty. However, methods dealing with structural uncertainties are not well-developed, even though these might have a significant impact on model results. This study investigates the impact of structural changes in a National Institute for Health and Care Excellence (NICE) single technology appraisal cost-effectiveness model of Erlotinib versus Best Supportive Care as a maintenance therapy for patients with non-small cell lung cancer. The manufacturer's model submission was criticised for having a "Markov" model not governed by transition probabilities. It considered an independent projective survival functions for progression-free survival and overall survival, which allowed a negative post-progression survival (PPS) estimate to appear in later cycle. **METHODS:** Using published summary survival data, this study adopted three approaches, covering both fixed- and time-varying, to estimate health state transition probabilities that are used in a restructured Markov model. **RESULTS:** Unlike for placebo, the parametric approach estimates post-progression probabilities and probabilities of death for Erlotinib differently than fixed-transition approaches. The best fitting curves are achieved for both PPS and probability of death across the time for which data were available, but the curves start diverging towards the end of this period. The alternative (Markov) model which extrapolates the curves forward in time suggests that this difference between a time-varying and fixed-transition becomes even greater. The alternative models produce an Incremental Cost-Effectiveness Ratio (ICER) of £54k -£66k per quality adjusted life year (QALY) gain, which is comparable to an ICER presented in the MS (£55k/QALY gain). **CONCLUSIONS:** The results from restructured alternative models do not suggest different cost-effectiveness results to those reported in the manufacturer submission; however, in terms of magnitude they vary. This variation in cost-effectiveness results produced by restructured models might be crucial for interventions falling near a threshold value.

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INVESTIGATING THE VALUE OF PATIENT LEVEL DATA TO INFORM ESTIMATES OF ADPKD PROGRESSION GENERATED WITHIN THE ADPKD OUTCOMES MODEL

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OBJECTIVES: Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder characterised by enlarged kidneys and declining renal function. ADPKD progression rates are heterogeneous, influenced by age, gender, renal size and genotype. Disease models often utilise progression rates derived from published studies. This study aimed to compare ADPKD progression, in terms of changes in total kidney volume (TKV) and renal function, modelled from summary versus patient-level data (PLD), and assess the consistency of predictions with trial observations. **METHODS:** Regression equations were derived from the TEMPO 3:4 trial placebo arm (natural history) to predict annual changes in TKV and estimated glomerular filtration rate (eGFR). Candidate covariates included age, gender, ethnicity, region/country, TKV and eGFR. Predictions were compared using the PLD regression equations or linear interpolation of summary rates of change in four patient categories. Finally, the model was initiated with published baseline patient profiles representing early and late disease from the HALT-PKD trials, and predicted progression compared to trial observations. **RESULTS:** For patients initiated with the average TEMPO 3:4 placebo profile, predicted eGFR trajectories based on PLD or summary data were similar (average decline: -5.3 and -5.1ml/min/1.73m2/year, respectively); however, TKV predictions deviated as TKV exceeded 2,500ml, with increasingly rapid growth predicted based on summary data. The model closely replicated ADPKD progression among patients with early disease; all predicted values within the 95% confidence interval of HALT-PKD observations. In patients with late disease, modelled baseline TKV of 1,000-1,500ml led to closest replication of eGFR observations (average decline: -3.2 to -4.4, versus -3.9ml/min/1.73m2/year during trial). **CONCLUSIONS:** Though predictions based on summary and PLD were consistent, the PLD regression equations produced more realistic results at extreme values. The availability of relevant PLD to describe the natural history of ADPKD progression provides a more robust foundation for disease and economic modelling than summary data alone.