37.2% for high cost-sharing; p<0.001). **CONCLUSIONS:** Patients in plans with no cost-sharing have greater adherence and are less likely to discontinue treatment in the 12-month period following DMT initiation. These results suggest that patients with MS are sensitive to the financial costs associated with DMT and may make treatment decisions based on this burden. Manufacturer co-pay assistance programs designed to reduce patient financial burden were not considered in this analysis. Therefore, these results may underestimate the effects of benefit design on medication adherence and persistence.

PND62

WHAT ARE THE KEY DRIVERS FOR CHANGING HTA DECISIONS? EXAMPLE OF ALZHEIMER'S DISEASE TREATMENT IN GERMANY, FRANCE AND UK

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OBJECTIVES: Since launch, HTA agencies from Germany, France and UK have repeatedly reviewed the use of Alzheimer's disease (AD) treatments and issued recommendations, which have changed over time. The aim of this study was to understand the drivers of agency decisions and whether these too have changed over time. **METHODS:** We reviewed HTA appraisals by IQWIG, HAS and NICE for three acetylcholinesterase inhibitors (AChEI) donepezil, galantamine, rivastigmine and memantine, an NMDA receptor antagonist from marketing authorisation to today and identified arguments leading to recommendations. **RESULTS:** Between 1997 and 2002, the EMA approved donepezil, rivastigmine and galantamine for mild to moderate AD and memantine for moderate to severe AD. We identified 2 multiple technology assessments (MTA) and 3 single technology assessments (STA) by IQWIG, 1 MTA and 16 STAs from HAS and 3 MTAs from NICE. Germany: IQWIG ascribed the AChEI class a modest clinical benefit. Following two negative assessments of memantine, the decision was reversed based on post-hoc analysis of initial registration studies. France: HAS initially assigned all treatments an important clinical added value (AMSR II) acknowledging high innovation. Later HAS reviewed the compounds in a new comparative setting (after withdrawal of tacrine) and assigned only a minor clinical added value (ASMR IV). UK: NICE recommended AChEIs in 2001, restricted their use in 2006 and in 2011 again recommended them, while memantine received two negative recommendations followed by a positive recommendation. The last review was based on additional data from randomized clinical trials and the Assessment Group's model demonstrating delay to institutionalisation. **CONCLUSIONS:** The agencies revised assessments based on post-marketing data. Differing national approaches led to different decisions: IQWIG emphasises patient relevant benefit, HAS the clinical added value versus similar medicinal products and NICE cost-effectiveness. Although agency decisions changed, decision drivers were consistent across evaluations.

PND63

DRUG PRESCRIPTION IN AND HOSPITALIZATION OF REFRACTORY FOCAL EPILEPSY PATIENTS IN THE GERMAN NEUROTRANSDATA (NTD) NEUROLOGISTS' NETWORK – IS THERE AN UNMET NEED?

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OBJECTIVES: To quantify annual drug costs and hospitalization rates (HR) of adult refractory focal epilepsy patients in Germany. **METHODS:** We retrospectively estimated the annual HR and medication for refractory focal epilepsy patients based on the NeuroTransData epilepsy database (input from 79neurologists, 34centers, 1240patients). Inclusion criteria (at least 1year of disease history; documentation and treatment period of at least 6months; treatment with at least 1anitepileptic drug [AED] in patient history; at least 1seizure during 6months of monitoring) led to the identification of 70 patients. Average ambulatory daily therapy costs among all prescribed drugs included were based on public prices (2011) considering clawbacks and average dosing (real world setting [RWS] vs. daily defined dosing [DDD]). HR were based on number of patients hospitalized. **RESULTS:** On average 2.1AEDs per patient were prescribed, mainly generic drugs or branded drugs close to loss of patent protection. Average daily costs per prescribed drug ranged from 0.65€ (Valproate) to 9.51€ (Lacosamid). Daily drug costs per patient ranged between 7.01€ (RWS) and 6.16€ (DDD). Annual total drug costs per patient were on average 2,557.44€. An ambulatory consultation rate of 2.1visits per patient within 6months was recorded. Average HR was 44%, taking into account various reasons: 56% emergency, 20% new adjustment for medication, 18% documentation of seizure, 4% rehabilitation, 2% pre-surgical diagnostics. Mean duration was 34.9 (CI: 20.2-49.6; median 17.8) days per patient hospitalized. Due to the potential selection bias and the low number of analysed patients these results must be seen as indicative. **CONCLUSIONS:** A 44% HR and a high average number of inpatient days (~1month) within 1year point to an unmet need for treatment optimization in refractory focal epilepsy patients. It indicates that patients receiving combination therapy of conventional drugs are often not well controlled, supporting the consideration of using more innovative drugs.

Neurological Disorders – Research on Methods

PND64

COST-MINIMIZATION ANALYSIS OF IFNB-1B AND FINGOLIMOD AMONG MULTIPLE SCLEROSIS PATIENTS IN GERMANY

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OBJECTIVES: Several disease-modifying therapies (DMTs) including IFNB-1b have been approved for patients with multiple sclerosis (MS) to delay disease progression and reduce the incidence of relapses. Fingolimod, the first oral formulation of DMT, was recently approved in several nations around the world including Germany. This study aims to conduct a cost-minimization analysis to estimate the cost impact of MS treatment with Fingolimod versus INFB-1b in Germany from the societal perspective. **METHODS:** A Markov model is developed to follow the natural history MS patients from time of diagnosis through disease progression and up to 20 years. MS patients receive either IFNB-1b or Fingolimod treatment but share the same efficacy on disease progression and relapse rate due to the absence of head-to-head comparison data. Fingolimod patients are assumed to have 10% higher treatment adherence due to the oral formulation. In the model, DMTs costs (IFNB-1b: €19,444/year and Fingolimod: €30,584/year) are based on AVP pharmacy retail price, while other cost items are estimated from published literatures or local databases. Main model outcomes include direct costs, indirect costs, and total costs. All costs are inflated to 2010 Euros and discounted annually at 5%. **RESULTS:** In the short-term analysis, Fingolimod costs additional €8,929 per patient in one year and €29,550 per patient in 5 years compared to IFNB-1b. Long-term analysis (20 years) shows that cost savings associated with IFNB-1b is €41,593 per patient, which mainly occurs when MS patients are still receiving treatment. The cost advantages of IFNB-1b in the long-term analysis are attributed to its lower drug cost (€50,342 vs. €92,873), serious adverse events management (€6.7 vs. €102.4), and clinical monitoring (€8.8 vs. €438.2). **CONCLUSIONS:** Compared to Fingolimod, MS treatment with INFB-1b leads to substantial cost savings from both societal and payer perspectives in Germany, with similar treatment effectiveness.

PND65

DESCRIBING AND COMPARING UTILITY FROM EQ-5D AND SF-6D IN A HUNTINGTON'S DISEASE POPULATION

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OBJECTIVES: The SF-6D and the EQ-5D are two widely used questionnaires to generate utility scores. The objective of this study is to describe and compare utilities derived from EQ-5D and SF-6D in Huntington's disease population. **METHODS:** We used data from Euro-HDB, a multicenter cross-sectional study conducted in France, Italy, Poland and Germany. In several subpopulations, with different degrees of severity, we used paired-samples t-test to identify significant differences and calculated the Pearson's correlation between SF-6D and the EQ-5D utilities. **RESULTS:** The overall sample included 278 patients: 96 from France, 32 from Gemany, 103 from Italy and 47 from Poland. For the overall population, mean utility scores were significantly different (EQ-5D: 0.34 (sd=0.446); SF-6D: 0.62 (sd=0.135); p<0.0001). However values were strongly correlated (r = 0.79, p<0.001). This difference was also significant when considering subpopulations (as discriminated with score of clinical motor scale, and depression scale), with higher values for SF-6D. The difference between EQ-5D and SF-6D utility scores was higher in severe population than in moderate for most of the studied criteria (severe motor impairment: EQ-5D: 0.62; SF-6D: 0.69; moderate motor impairment: EQ-5D: 0.00; SF-6D: 0.51). The SF-6D scores distribution was found to be approximately normal whereas the EQ-5D distribution was negatively skewed. **CONCLUSIONS:** In our study, EQ-5D tends to generate lower scores in all Huntington's disease subpopulations. EQ-5D appears to be more sensitive than SF-6D. The choice of utility measure is likely to have a strong impact on incremental cost-effectiveness ratios of interventions slowing the progression of Huntington's disease.

PND66

CROSS-CULTURAL ADAPTATION AND VALIDATION OF THE BRAZILIAN VERSION OF THE FATIGUE SEVERITY SCALE (FSS)

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OBJECTIVES: The aim was to perform a cross-cultural adaptation and validation of the Fatigue Severity Scale (FSS) for use in Brazilian patients with myopathy and who complains of precocious muscular fatigue. **METHODS:** The FSS presents nine items measured on a Likert scale ranging from 1 (completely disagree) to 7 (completely agree), where higher scores indicate higher level of fatigue. The process of cross-cultural adaptation included: two independent translations for Portuguese spoken in Brazil; the development of a consensual translated version; application in a pilot group (n=14) of patients with myopathy; evaluation by an expert committee for content validation; a back-translation by one bilingual translator whose native tongue was English, but who was fluent in Brazilian Portuguese. The two English versions (original and back translated) were analyzed by two of the authors and a final Brazilian version was obtained. Twenty one patients with muscular disease following at the outpatient clinic from a University Hospital answered the Brazilian version of the FSS, the visual analogue scale (VAS) and the Chalder fatigue questionnaire (CFQ). The following analyses were performed: exploratory factorial analysis; internal consistency (Cronbach's alpha); construct validity through of the correlation with VAS and CFQ (physical and mental components). **RESULTS:** The FSS scale obtained in the process of cross cultural adaptation was comprehensible to individuals in the pilot population. The twenty one patients who participate in the validation process were aged 21 to 65 years. The exploratory factor analysis determined one factor, as the original version. Reliability analysis indicated satisfactory internal consistency (0.93). Construct validity of the FSS (total score) with VAS and CFQ demonstrated moderate correlations (0.60 and physical=0.56, respectively). The FSS didn't correlate with mental component of the CFQ (0.31).

CONCLUSIONS: The FSS scale is an instrument reliable and valid to measure muscular fatigue in Brazilian patients with myopathy.

PND67

A MIXED-EFFECTS PIECEWISE LINEAR MODEL OF THE RATE OF LUNG FUNCTION DECLINE BEFORE AND AFTER THE CLINICAL USE OF DORNASE ALFA IN AN OBSERVATIONAL STUDY OF CYSTIC FIBROSIS

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OBJECTIVES: To evaluate lung function decline before and after the initiation of dornase alfa (DA) through a multivariable mixed-effects piecewise linear model using data from the Epidemiologic Study of Cystic Fibrosis (ESCF). **METHODS:** Patients aged 8-38 years enrolled in ESCF for 2 or more years prior to initial treatment with DA were selected if they remained on treatment for at least 2 years. A comparator group included cystic fibrosis patients not yet reported to have received DA. FEV1 percent predicted (pp) was analyzed before and after an index measurement within 30 days of either DA initiation (DA group) or an encounter within 1 year following the 8th or subsequent even-numbered birthday (comparator group). For each patient, we fit a regression line to FEV1 pp separately for the pre-index and post-index periods (both 2 years in duration) using a mixed-effects piecewise linear model adjusted for age, gender, pulmonary exacerbations, respiratory therapies, and nutritional supplements. Patients were categorized by age group or by age-adjusted deciles of the index FEV1 pp. **RESULTS:** The DA group (n=2,230) had a lower FEV1 pp at index and a more rapid decline during the pre-index period. There was an acute improvement in FEV1 pp (change in intercept) associated with the initiation of DA therapy. Furthermore, the mean rate of FEV1 pp decline was more attenuated for the DA group than for the comparator group (n=5,970) across age groups and deciles. **CONCLUSIONS:** The use of DA for a 2-year period is associated with both an acute improvement in FEV1 pp (previously shown in clinical trials) and a reduction in the rate of FEV1 pp decline (shown for the first time). These results demonstrate the value of using mixed-effects piecewise linear models in observational studies to evaluate the effect of instituting a therapy on both the slope and intercept of a continuous outcome.

PND68

SOCIAL ECONOMIC BURDEN AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH RARE DISEASES IN EUROPE (BURQOL-RD PROJECT). METHODS OF SELECTION OF 10 DISEASES FOR A EUROPEAN SURVEY

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OBJECTIVES: The BURQOL-RD project is intended to develop a disease based model capable of quantifying the socio-economic burden and Health-Related Quality of Life (HRQOL) for patients with rare diseases (RD) and their caregivers in Europe. We described the methodology used to select a set of 10 RD to be approached in a pilot study. **METHODS:** BURQOL-RD project counts with 20 partners, from 8 European countries: Spain, UK, France, Germany, Sweden, Italy, Hungary and Bulgaria. A two-round Delphi process was used to generate consensus in the selection of the 10 RD among the project participants. The wide variability and dispersion of the responses received in the two Delphi rounds of prioritization suggested that an additional procedure should be implemented to improve the representativeness of selected diseases. A Lewis Carroll's trilateral diagram was applied based on three determinants. **RESULTS:** The two rounds of Delphi panel yielded into a prioritised list, to which the Carroll diagram was applied, taking into account three determinants: prevalence, availability of effective treatment and need for carer. The final set of RD was obtained to be targeted in the pilot study of BURQOL-RD: Cystic Fibrosis, Prader-Willi Syndrome, Haemophilia, Duchenne Muscular Dystrophy, Epidermolysis Bullosa, Fragile X Syndrome, Sclerodermia, Mucopolysaccharidosis, Juvenile Idiopathic Arthritis and Histiocytosis. **CONCLUSIONS:** This methodology permitted to obtain an equilibrated set of RD for the pilot study of BURQOL-RD project. The model that will be generated will not only be suitable to apply in a wide range of RD but it will also be sufficiently flexible to identify and adapt to the challenges faced by the different health and social care systems of EU member states.

Urinary/Kidney Disorders – Clinical Outcomes Studies

PUK1

BELATACEPT VERSUS TACROLIMUS: RESULTS OF AN INDIRECT ANALYSIS FROM A SYSTEMATIC REVIEW OF IMMUNOSUPPRESSIVE THERAPIES FOR KIDNEY TRANSPLANT RECIPIENTS

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OBJECTIVES: To systematically identify and summarise the evidence of renal transplant outcomes, toxicity and adverse effects in order to determine the most effective options. In particular, comparing tacrolimus, the cornerstone of renal transplantation therapy, with newer therapies that have been introduced since 2003. **METHODS:** An electronic literature search of MEDLINE, Current Contents and the Cochrane Library databases was conducted, plus manual reference checks of all articles involving controlled trials of kidney transplants and immunosuppressive therapy between 2003 and July 2010. Studies were assessed for eligibility and quality by two reviewers who extracted data independently. Studies were classified according to CNI avoidance or reduction, steroid avoidance, and induction therapies. Results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where necessary, indirect comparison techniques were used to compare different forms of tacrolimus with belatacept. **RESULTS:** Thirty-five studies from an initial list of 2895 citations were included in the analysis. Results show CNI avoidance leads to higher incidence of acute rejection (RR 2.52, 95% CI 1.11–5.75), which is a known predictor for graft loss, but reduced chronic allograft nephropathy. Tacrolimus produces better rejection prophylaxis compared with ciclosporin (RR 0.38, 95% CI 0.21–0.70), and ciclosporin produces lower acute rejection compared with belatacept (RR 0.32, 95% CI 0.19–0.55). Indirect analysis shows that tacrolimus is superior to belatacept in acute rejection prophylaxis (RR 0.18, 95% CI 0.08–0.39), but leads to more cases of a decrease in glomerular filtration rate (GFR) (RR 1.37, 95% CI 0.92–2.03); however, the long-term impact of a reduction in GFR in the context of a CNI-free regimen is not clear at present. **CONCLUSIONS:** Direct and indirect comparisons demonstrate that CNIs, and in particular tacrolimus, remain superior even against more recent compounds for preventing acute rejection. However, more research needs to be done to find the optimum combination of therapies.

PUK2

COMPARATIVE EFFECTIVENESS OF INVESTIGATIONAL COMPOUND FERUMOXYTOL FOR THE TREATMENT OF IRON DEFICIENCY ANAEMIA IN CHRONIC KIDNEY DISEASE: SYSTEMATIC REVIEW AND MIXED TREATMENT COMPARISON

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OBJECTIVES: To evaluate the comparative effectiveness of investigational compound ferumoxytol for the treatment of iron deficiency anaemia (IDA) associated with chronic kidney disease (CKD) compared to alternative iron replacement therapies (IRT). Primary interest was the improvement in haemoglobin (Hb) from baseline levels. **METHODS:** A comprehensive systematic review was conducted to identify any randomised controlled trials investigating the efficacy of IRTs for the treatment of IDA in CKD where efficacy is defined as Hb change from baseline and IRTs included intravenous (IV) and oral treatments. Twelve electronic databases were searched up to November 2010 (language unrestricted). Two reviewers independently assessed each identified reference and conducted subsequent data extraction. Method quality of each included trial was also independently assessed in accordance with NICE guidelines. A standard meta-analysis comparing oral iron to ferumoxytol was initially conducted, reflecting the trial programme. The full network of evidence that included IV and oral iron therapies was synthesised using a mixed treatment comparison (MTC). The random effects model showed 'predicting superiority' to the fixed effects model and was thus utilised. Mean efficacy was estimated through analysing standardised effect sizes of trials and back-transforming data to Hb values via weighted average standard deviation. **RESULTS:** Seventeen published trials and one unpublished clinical study provided the heterogeneous trial base for MTC analysis. Ferumoxytol was significantly favoured when compared to oral iron therapy by conventional meta-analysis (0.61; 95% CI=0.44,0.79; P value=<0.0001) which was supported by results from the MTC efficacy analysis (0.48; 95% CI=−1.24,2.2). Significant differences in efficacy were not observed between ferumoxytol and any of the alternative IV iron therapies. **CONCLUSIONS:** The results from the conventional meta-analysis showed that the model favoured investigational compound ferumoxytol, in terms of increasing Hb, in comparison to oral iron therapy and suggested a modelled equivalence to currently approved alternative IV iron treatments.

PUK3

SOURCES OF HETEROGENEITY AMONG OVERACTIVE BLADDER CLINICAL TRIAL ESTIMATES OF TOLTERODINE AND FESOTERODINE REDUCTIONS OF URGENCY URINARY INCONTINENCE EPISODES RELATIVE TO PLACEBO

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OBJECTIVES: Explore potential sources of heterogeneity among estimates of tolterodine (TOL) and fesoterodine (FESO) efficacy relative to placebo (PBO) in patients with overactive bladder and urgency urinary incontinence (UUI) from randomized clinical trials (RCTs) published from 2001 – 2010. **METHODS:** RCTs evaluating TOL 4mg, solifenacin 5mg and/or 10mg, or FESO 4mg or 8mg compared to PBO reporting mean reduction of UUI episodes/d from baseline to endpoint were identified. Treatment effects (treatment response minus PBO response) and PBO responses were tested for heterogeneity using Cochran's Q statistic. Where heterogeneity was present, other study variables (baseline UUI, baseline micturitions, gender, age, diary evaluation days, publication year, and study duration) were evaluated for potential confounding using linear regression methods. **RESULTS:** Statistical heterogeneity was found among the 17 PBO responses (mean reduction of UUI) of the included studies. PBO response increased with publication year, which accounted for more than 27% of response variation. Publication year ($p<0.02$), gender ($p<0.003$), and study duration (6-week vs. other) ($p<0.006$) were significant predictors of PBO response (adj. R2=0.6261). TOL and FESO 8mg treatment effect estimates were also heterogeneous. Among the nine TOL trials, treatment responses remained constant over publication year while PBO responses increased, resulting in a net decline in TOL treatment effect ($p=0.0928$). The majority of this decline was explained by publication year and study duration (adj. R2=0.7703). The four FESO 8mg UUI responses also displayed a publication year-dependent decrease leading to a decreasing treatment effect relative to PBO. However, this trend was almost fully predictable by differential baseline UUI episodes (adj. R2=0.9721). **CONCLUSIONS:** Publication year, gender, 6-week duration, and baseline UUI were found to be significant predictors of PBO response or treatment effect. Additional research should be done to understand why PBO response has increased over time