disagree that innovation in health care is worthwhile; the tremendous technological success in pharmacological treatment of HIV patients is a case in point. On the other hand, a relatively large number of "me-too" entries in the pharmaceutical market and the diminishing productivity of R&D sector call for robust methodologies, which could distinguish high-value, breakthrough products. Sensitivity analyses of cost-effectiveness studies should be made pivotal in decision-making process in order to ensure efficient diffusion of innovation.

PRM243

SURVEY DESIGN IN THE ASSESSMENT OF THE IMPLEMENTATION OF RISK MINIMISATION MEASURES FOR MEDICINAL PRODUCTS

Prieto L, Hidalgo-Simon A, Arlett P

European Medicines Agency, London, UK

The introduction of the risk management plan (RMP) has ensured greater proactivity to the pharmacovigilance and post-authorisation benefit risk assessment of human medicines. An RMP may include risk minimisation measures (RMM), public health interventions intended to prevent the occurrence, or reduce the impact of adverse drug reactions associated with the exposure to a drug. The new EU legislation on pharmacovigilance explicitly requires the active monitoring of the outcome of RMM, placing obligations on regulators and industry for this purpose. In this respect, the European Medicines Agency's good pharmacovigilance practices module dedicated to the practical implementation of the legislation on the evaluation of the effectiveness of RMM foresees a dual evidence approach. This approach builds on the assessment of two distinct levels of evidence: the actual implementation of the RMM, and the attainment of its final objective(s). The approach requires research encompassing analysis of implementation (process indicators), and traditional epidemiological research addressing the attainment (final outcome indicators) of RMM. Surveys are usually involved in the assessment of process indicators, in particular when RMM imply the provision of educational information to health care professionals (HCP) and the surveys are intended to measure what the HCP have learned. This paper aims to conceptualise the construction of surveys designed for the analysis of implementation of RMM. Such surveys should be developed following the principles of content validation. This requires a body of relevant questions (items), the sample population to which it will be administered, and a test plan. The test plan includes the type of items to be used, the number of items, the length of administration, how it is to be administered, and how it is to be scored and analysed in terms of item difficulty and discrimination. The paper concludes with a checklist to assist stakeholders in designing surveys for RMM assessment purposes.

DISEASE-SPECIFIC STUDIES

NEUROLOGICAL DISORDERS – Clinical Outcomes Studies

PND1

DISEASE BURDEN IN EPILEPSY ASSOCIATED WITH TUBEROUS SCLEROSIS COMPLEX: SYSTEMATIC REVIEW

Blieden M[1], Parker L[1], Foster T[1], Segal S[2], Magestro M[2]

[1]*Evidera, Lexington, MA, USA,* [2]*Novartis Pharmaceuticals Corporation, Florham Park, NJ, USA*

OBJECTIVES: To summarize literature on the burden of epilepsy in tuberous sclerosis complex (TSC); TSC is a genetic disease characterized by behavioral disorders, benign tumors in multiple organs, and neurological manifestations including epilepsy. **METHODS:** A systematic search of keywords for TSC and burden of illness was conducted in MEDLINE- and EMBASE-indexed publications from 5/2000-1/2013, and non-indexed materials. **RESULTS:** In total, 83 articles on TSC-associated epilepsy were included. Up to 93% of TSC patients have epilepsy, with severe forms more common than in non-TSC epilepsy patients (infantile spasms, 35-57% vs. 9%; generalized tonic-clonic or grand mal seizures, 37% vs. 7%; complex focal seizures, 87% vs. 33%). Seizure onset is early (median age: 7 months, 82% by age 3). TSC2 gene mutations and cortical tubers, common brain malformations in TSC, are risk factors for early onset and greater severity of seizures. TSC-epilepsy patients have significant disabilities, including high rates of autism spectrum disorders (13-30%) and cognitive impairment/delay (62-80%). Although data are not available on long-term outcomes, early seizure control may reduce cognitive impairment and autism symptoms. Vigabatrin is a first-line treatment option for TSC-associated infantile spasms and focal seizures in infants, but poses a risk of serious retinal toxicity. Other anti-epileptic drugs are available as second-line options; most patients still require polytherapy, and 62% have refractory epilepsy that can necessitate surgery. With high rates of medication use, hospitalizations, and surgeries, TSC-epilepsy patients may consume substantial health care resources, particularly during the first 5 years post-diagnosis. Longitudinal trends in resource use, direct and indirect costs, and treatment patterns for TSC-epilepsy are largely absent from the literature. **CONCLUSIONS:** TSC-epilepsy is common and may be severe, with presentation early in childhood and long-term morbidity. True disease burden to patients, caregivers, and payers remains unknown given substantial data gaps in longitudinal clinical outcomes, treatment patterns, and costs.

PND2

POTENTIAL PREDICTORS OF ALZHEIMER'S DISEASE: AN ANALYSIS WITH THE QUEBEC PROVINCIAL DRUG REIMBURSEMENT PROGRAM DATABASE

Lachaine J[1], Lambert-Obry V[1], Dionne PA[2]

[1]*University of Montreal, Montreal, QC, Canada,* [2]*Pfizer Canada, Kirkland, QC, Canada*

OBJECTIVES: To identify potential determinants of Alzheimer's disease (AD) by analyzing past medical history in terms of previous diseases or treatment exposures of patients with AD compared to patients without the disease, using the Quebec provincial drug reimbursement program database (RAMQ). **METHODS:** This retrospective study included patients covered by the RAMQ who had at least one diagnosis of AD (ICD-9 code 3310) or have received at least one script for an AD medication (donepezil, rivastigmine, galantamine or memantine) from January, 1985 to December, 2011. A control group of patients without AD was created on a 1:1 ratio and matched for age, gender and geographic location. The index date was defined as the date of the first AD diagnosis or the first script for AD medication whichever comes first. Prevalence of diseases and treatment exposures in the years preceding the index date were analyzed according to the occurrence of diseases (ICD-9 codes) and medication utilization (AHFS codification) between AD patients and the control group. **RESULTS:** Data were obtained for a random sample of 34,086 AD patients (mean age of 78.5 years [SD=8.0], 65.2% females). A higher proportion of patients had a diagnosis of organic psychotic conditions (49.6% vs. 9.2%, p<0.001), other psychoses (21.9% vs. 8.6%, p<0.001) and neurotic disorders, personality disorders and other nonpsychotic mental disorders (69.1% vs. 55.4%, p<0.001) in the AD group compared to the control group. Furthermore, a greater number of patients used psychotropic drugs (53.5% vs. 35.9%, p<0.001) and anxiolytics, sedatives and hypnotics (70.3% vs. 65.9%, p<0.001) in the AD group than in the control group. **CONCLUSIONS:** Comorbidities' frequency was higher in AD patients for several diseases and treatments, particularly for mental disorders-related diagnoses and medications.

PND3

EFFICACY OF FINGOLIMOD IN DELAYING CONFIRMED DISABILITY PROGRESSION IN PATIENTS FAILING PRIOR TREATMENT: A MARKOV MODEL APPLICATION TO ESTIMATE TIME TO DISABILITY HEALTH STATES

Bergvall N[1], Rathi H[2], Nixon RM[1], Thom HHZ[3]

[1]*Novartis Pharma AG, Basel, Switzerland,* [2]*Novartis Healthcare Pvt.Ltd., Hyderabad, India,* [3]*MRC Biostatistics Unit, Cambridge, UK*

OBJECTIVES: To estimate the efficacy of fingolimod versus placebo on confirmed disability progression (CDP) and on time to severe disability health states in patients with relapsing–remitting multiple sclerosis (RRMS) failing prior treatment. **METHODS:** Patients failing prior treatment were defined as: 1) ≥1 relapse in the previous year and either ≥1 gadolinium-enhancing T1 lesion or a T2 lesion count ≥9 at baseline, or 2) equal or more relapses in the year prior to baseline compared with the previous year. Hazard ratios (HR) for 3-month and 6-month CDP, measured using Expanded Disability Status Scale (EDSS) scores, were estimated using Cox proportional hazards models. Both per-protocol definitions of CDP and revised definitions used in other trials were analysed. Time from EDSS score 0 to scores of 4 or 6 and to conversion to secondary progressive MS (SPMS) were estimated by fitting a multi-state Markov Transition model to individual patient data from the pooled FREEDOMS placebo groups (HRs accounted for treatment effects) and the London Ontario cohort (SPMS and RRMS–SPMS transitions). **RESULTS:** Using both definitions of treatment failure, fingolimod reduced the risk of 3-month CDP (per-protocol) by 35% (definition 1: HR: 0.65; p<0.05) and 34% (definition 2: HR: 0.66; p<0.05) versus placebo. The corresponding HRs for 6-month CDP were 0.61 (p=0.06) and 0.60 (p<0.05). HRs were generally lower using the revised CDP definition. The Markov Transition model, assuming a 40% reduction, estimated that fingolimod delays the median time to EDSS 4 (2.2 years, 61% increase), EDSS 6 (3.3 years, 52% increase) and SPMS (4.5 years, 62% increase) compared with placebo. **CONCLUSIONS:** Fingolimod is highly efficacious in delaying CDP in patients failing prior treatment, and our modeling approach suggests that this translates into a meaningful delay in time to severe disability health states.

PND4

COMPARING THE EFFICACY OF FIRST AND SECOND GENERATION DISEASE-MODIFYING THERAPIES FOR RELAPSING-REMITTING MULTIPLE SCLEROSIS: A NETWORK META-ANALYSIS

Fogarty E[1], Schmitz S[2], Walsh C[2], Barry M[1]

[1]*National Centre for Pharmacoeconomics, Dublin, Ireland,* [2]*Trinity College Dublin, Dublin, Ireland*

OBJECTIVES: As the number of available disease-modifying therapies (DMT) for relapsing-remitting multiple sclerosis (RRMS) expands, consideration of all evidence on comparative efficacy of newer second generation therapies with established first generation therapies is required to inform clinical care and health policy. This network meta-analysis (NMA) estimates the relative efficacy of DMT in reducing relapses and slowing short-term progression of disability in RRMS. **METHODS:** A systematic review of RCTs of interferon-beta, glatiramer acetate (first generation DMTs), natalizumab, alemtuzumab, fingolimod, teriflunomide, laquinimod, and BG-12 (second generation DMTs) compared with each other or with placebo for the treatment of RRMS, identified 20 eligible RCTs (n=14610). A random-effects NMA model was used to calculate relative annualized relapse rate (ARR) and hazard ratio (HR) of short-term disability progression. **RESULTS:** Statistically significant reductions in ARR versus placebo, between 24% - 69% for second generation DMTs and 16% - 33% for first generation DMTs were found. Alemtuzumab, natalizumab, fingolimod, and BG-12 were significantly more efficacious than other DMTs in reducing ARR. There was greater uncertainty associated with DMT efficacy in reducing short-term disability progression. Significant improvements over placebo in reducing short-term disability progression were restricted to second generation DMTs alemtuzumab, natalizumab, fingolimod, laquinimod, BG-12, and teriflunomide 14mg (HR 0.27 - 0.54). No statistically significant improvements in short-term disability progression were exhibited by first generation DMTs and teriflunomide 7mg. **CONCLUSIONS:** The growing number of innovative second generation DMTs offers the potential of therapeutic advances in reducing relapse rates in RRMS, with less certain benefits on short-term disability progression. Despite these potential advantages, the relative position of second generation DMTs on the RRMS treatment landscape remains to be defined, due to potentially serious side effects, limited long-term safety data and their high cost.

PND5

EFFECTIVENESS OF THE EARLY PSYCHOSOCIAL INTERVENTION ON INSTITUTIONALIZATION OF PATIENTS WITH MILD ALZHEIMER'S DISEASE AND CAREGIVERS' QUALITY OF LIFE – AN ALSOVA STUDY

Martikainen JA[1], Kautiainen H[2], Väätäinen S[1], Välimäki T[1], Hongisto K[1], Hallikainen I[1], Sivenius J[1], Soininen H[1], Koivisto A[1]

[1]*University of Eastern Finland, Kuopio, Finland,* [2]*Medcare Foundation, Äänekoski, Finland*