PRM38	MEASUREMENT PROPERTIES OF THE SPANISH VERSION OF THE PEDIATRIC PROMIS FATIGUE ITEM BANK
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OBJECTIVES: Fatigue is common among children with chronic conditions. In order to compare results across languages, a requirement for many clinical trials, one must ensure measurement is not biased by language. This paper reports the psychometric properties of the Spanish version of the pediatric PROMIS (Patient Report Outcome Measurement Information System) fatigue item bank (Spanish-PedsFrib). Developed via a collaborative effort funded by the National Institutes of Health of the United States, PROMIS allows for comparisons across domains and conditions for both adults and children. METHODS: Data from 605 Spanish-speaking participants recruited from a US general population panel, were analyzed. Average age was 12.3 years and 45.5% were female. Participants completed the 23-item Spanish-PedsFrib, translated from English via a rigorous methodology (2 forward translations, 1 reconciliation, 1 back-translation, review by bilingual experts, and cognitive debriefing). Psychometric analyses included confirmatory factor analysis (CFA) to evaluate unidimensionality (criteria: comparative fit index CFI > 0.95, RMSEA < 0.08, MI < 1.0), residual correlations to evaluate local dependency (criterion: r < 0.15), S-G² and S-χ² to evaluate item fit (criterion: p > 0.01). Graded Response Model as implemented in MULTLOG was used to estimate item parameters, and LORIDIR (R free ware) was used to evaluate differential item functioning between the Spanish and English versions (criteria: p < 0.05). RESULTS: CFA results supported unidimensionality of these 23 items: CFI = 0.959, RMSEA = 0.056, residual correlation absolute values ranged from 0 to 0.05, and R² ranged from 0.69 and 0.87. One item dropped from the pool due to floor effect decision. Six items (measuring more severe fatigue) exhibited significant DIF. Correlation between scores with and without DIF candidate items was 0.97. CONCLUSIONS: Excellent psychometric properties of the Spanish version of Spanish-PedsFrib were evidenced. Conclusions from this paper will be used to inform the future validation of the English and Spanish versions. Currently, more translations are in progress.

RESEARCH ON METHODS - Statistical Methods
PRM39	SURVIVAL CURVE CONVERGENCES AND CROSSING: A THREAT TO VALIDITY OF META-ANALYSIS?
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OBJECTIVES: When data from survival analysis are summarized in meta-analysis, they are usually based on the number of events at the end of the study. This will bias the estimates of differences in survival unless the relative hazards are relatively constant (the proportional hazards assumption). The aim of this study was to explore this assumption by estimating the frequency of convergences and crossings of survival curves. METHODS: We reviewed all publications in Annals of Internal Medicine, British Medical Journal, JAMA, New England Journal of Medicine (NEJM) and The Lancet for 2007 and identified studies that included survival graphs. We extracted the following data from included studies: type of disease, type of exposure, sample size and number of events, maximum follow-up time, number and timing of survival curve convergences and crossings, and whether Cox regression and log-rank tests had been performed. RESULTS: Among 175 included studies, 56 had survival curve convergences and 47% crossings. 38% of the crossings occurred later than halfway through the study (60% for convergences). The proportion of crossings by type of disease was 46% for cardiovascular disease, 38% for cancer and 53% for other diseases. Among studies with survival curve crossings, Cox regression was performed in 66% and log-rank test in 70% of the studies. Only 31% of studies did not use adjustment for time-varying covariates. CONCLUSIONS: Survival curve convergences and crossings are common in medical research. Effectiveness estimates based on end of study results will likely be biased unless convergences and crossings are accounted for, and this bias will carry over to meta analyses of individual studies. Researchers frequently employ Cox modeling when the proportional assumption is not met or use log rank tests when other test would be more appropriate.

PRM40	APPLYING STRATIFICATION ON TIME TO OVERCOME TIME-VARYING COVARIATES EFFECT ON COX PROPORTIONAL HAZARDS MODELS
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OBJECTIVES: Cox proportional hazards models are widely used in the analysis of survival data from clinical trials to explain the effects of prognostic factors on survival time. The model assumes proportionality of prognostic factors over time. Prognostic factor values, however, are often not constant over time, causing time-varying covariate (TVC) effects. In order to overcome this problem, a helpful method is to incorporate stratification on time. This study estimates the survival of chronic renal failure (CRF) patients using the above method. METHODS: This analysis was conducted on data from 145 patients in a Malaysian government hospital. The assumption of proportionality was analyzed using log cumulative hazards curves plotted against log time (log-minus-log) and Schoenfeld residuals and scaled Schoenfeld partial residuals. TVC was analyzed by the interactions of prognostic factors with log time. Violation of the proportionality assumption was overcome by stratification on time. RESULTS: Median survival time of CRF patients in the study was estimated at 4.5 years. The significant prognostic factors were ex-smokers (p = 0.043), current smokers (p = 0.035) and post-renal failure hypertensive patients (p = 0.054). The proportionality assumption was violated in the ex-smokers’ factor as shown by log-minus-log and Schoenfeld residuals and scaled Schoenfeld partial residuals. Stratification on time at 0.8 years was applied to correct the problem. CONCLUSIONS: Survival analysis in this study using the Cox proportional hazards model was affected by the TVC effect on the ex-smokers as a prognostic factor. Stratification on time was able to overcome this problem.

RESEARCH ON METHODS - Conceptual Papers
PRM42	MULTIPLE CRITERIA DECISION ANALYSIS FOR HEALTH TECHNOLOGY ASSESSMENT
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OBJECTIVES: This paper will discuss the different methods of multi criteria decision analysis (MCDA) that could be used in health technology assessment (HTA) and their relative merits. Description: The current practice of health technology appraisal is based on the incremental cost-effectiveness ratio (ICER) i.e. the incremental cost per quality adjusted life year (QALY) gained by recipients of treatment. Even though other factors (e.g. severity, life saving, etc) are considered along with ICERs, there is concern that its approach may fail to capture other important sources of value. METHODS: MCDA is aimed at supporting decision makers faced with evaluating alternatives taking into account multiple, and often conflicting, criteria in an explicit manner. An overview of MCDA is provided and is compared against the current health technology appraisal processes. A number of important questions are addressed to identify the most appropriate MCDA method that might be used in HTA. Questions include: 1) What criteria should be incorporated? 2) Which criteria will be weighted? 3) How should we identify the weights? 4) What should the ‘basic’ cost-effectiveness threshold be? 5) How do we evidence converge contradictions? 6) How do we evidence cross contradictions? 7) What are the ethical considerations? 8) What are the implications for HTA? To answer these questions, comparisons and assessment of the methodological issues that would be raised by the use of MCDA in health technology assessment (HTA). RESULTS: Most of the proposed MCDA approaches in literature use the same technique (weighted sum approach), however, more flexible approaches that are relevant to health technology appraisal and value based pricing (VBP). CONCLUSIONS: There is general practical issues that might arise from using this MCDA approach in the HTA process and further research needs to be performed to address the issues identified in order to ensure the success of this MCDA technique in the appraisal process.

PRM44	ROLES AND SELECTION OF COMPARATIVE TREATMENT(S) IN THE ASSESSMENT OF NEW DRUG REIMBURSEMENT AND PRICING APPLICATION TO TAIWAN NATIONAL HEALTH INSURANCE (NHI)
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The Principles on Drug Reimbursement Price Approval (PDRPA) is the basis for pricing new pharmaceuticals for NHI reimbursement in Taiwan. PDRPA describes the scope of comparative treatments and defines the 3Categories of new drug as: 1 (breakthrough), 2A (moderate improvement), and 2B (similar) based on the comparative effectiveness of new drug to the current therapies, which links to the pricing decision method used. The selection of comparator is crucial in technology assessment and has profound influence on the pricing decision. Hereby we explicitly describe the selection ratione and roles of comparator. To do this, the authors firstly presented the rationale of comparator selection, the following 8 features of a comparator are considered: 1) indication(s) approved by department of health Taiwan; 2) associated reimbursement guidance; 3) ATC (Anatomical Therapeutic Chemical) classification; 4) clinical guidance for comparative treatment; 5) ATC (Anatomical Therapeutic Chemical) classification; 6) NHI reimburse price; 7) prices of comparator in the 10 reference countries; and 8) recent utilization in NHI. Clinical relevant and appropriateness are the priority of comparator(s) selection. To be qualified as class 1 or 2A new drug, the currently best therapy should be used as comparator. Then one of the 6 pricing methods will be decided to reckon the reimbursement price of the new drug, or with no reimbursement guidance on using the new drug and/or the decision to initiate price-volume agreement or (financial) risk sharing negotiation with the pharmaceutical company. Five possible roles of the comparator(s) would play in the assessment: 1) to justify the comparative effectiveness to the new drug; 2) to calculate the price of new drug; 3) to evaluate the net budget impact; 4) as reference treatments for reimbursement guidance; and 5) be used in pharmacoeconomic study.

PRM44 CLINICAL AND COMPARATIVE ECONOMIC VALUE - A NOVEL PHARMACOECONOMIC ANALYSIS EMBEDDED IN THE DRUG DEVELOPMENT PROCESS
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OBJECTIVES: Pharmaceutical companies are under pressure to assess the eco- nomic value of their pipeline assets. Pharmacoeconomic (PE) analysis can be em- ployed to improve the decision-making process by providing robust estimations of comparative economic value before the commercial launch. Clinical and Comparative Economic Value (CCEV) methodology has been developed to provide insights into the sources of economic values of innovative products (drugs, devices, ser- vices) to inform critical decisions across the product life cycle. METHODS: A multistate disease model was developed to simulate the major clinical events in the dis-