methods. Often it is mentioned that in order to obtain unbiased estimates based on indirect comparisons the distribution of characteristics of the patients included in the different trials needs to be similar, as well as the study design. By means of directed acyclic graphs (DAGs), which are often used in epidemiology for inferences, it is explained that indirect and mixed treatment comparisons are biased when differences in patient characteristics and trial design do act as an effect modifier of the treatment effect. Furthermore, the graphs can be used to differentiate between heterogeneity, selection, and confounding bias. DAGs for indirect comparisons of RCTs are compared with DAGs for head-to-head randomized designs and meta-analysis of RCTs.

RESEARCH ON METHODS & CONCEPTUAL PAPERS—Cost Studies

METHODS FOR ESTIMATING CONFIDENCE INTERVALS OF PER MEMBER PER MONTH (PMPM) UTILIZATION RATES

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OBJECTIVES: Per member per month (PMPM) utilization rates are commonly reported in the medical literature to compare differences in costs and other outcomes across various health care technologies and interventions. A limitation of PMPM estimates is that a confidence limit around the point estimate is not obvious or available from standard statistical software. Our objective is to demonstrate various methods of calculating confidence intervals for PMPM utilization rates. METHODS: Several methods were used to estimate confidence intervals surrounding PMPM estimates including Fieller’s method and Monte-Carlo (MC) simulation. Women with at least one prescription fill for alendronate, risedronate, or ibandronate during 2006 in a large managed care data set were used as a sample to generate PMPM estimates and 95% confidence intervals for bisphosphonate drug cost, all hospitalization cost, hospital days, and number of hospital admissions during the calendar year of 2006. RESULTS: There were 34,675 women in our sample. The PMPM estimate of bisphosphonate drug cost was $23.48. The 95% confidence intervals generated by the Fieller and MC methods were ($22.53, 263.03) and ($227.74, 259.99), respectively. The PMPM estimate of hospital days was 0.108 days: Fieller and MC 95% confidence intervals were (0.098, 0.118) and (0.100, 0.116), respectively. The PMPM point estimate for number of hospital admissions was 0.0137: Fieller and MC 95% confidence intervals were (0.0131, 0.0142) and (0.0133, 0.0142), respectively. CONCLUSION: The Fieller and MC simulation methods produced similar confidence intervals for PMPM estimates for each of the outcomes of interest. Use of these methods would improve the utility of PMPM point estimates in comparing health care technologies.

AN ANATOMY OF PHARMACEUTICAL COST-UTILITY ANALYSES, 1976–2005

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OBJECTIVE: To review and critically evaluate published cost-utility analysis (CUA) research on pharmaceuticals for the past three decades. METHODS: We examined data from the Tufts-NEMC Cost-Effectiveness Analysis Registry www.tufts-nemc.org/cearegistry/), which contains detailed information on over 1100 CUA and 3000 cost-utility ratios (in US$2005) published from 1976–2005. RESULTS: Of 1164 CUA published through 2005, 518 (44.5%) pertain to pharmaceuticals. The proportion of all CUA that focus on pharmaceuticals increased from 32% prior to 1990 to 48% from 1990–2005. U.S.-based investigators account for 53.6% of the total (47.5% of pharmaceutical CUA), with the proportion of all CUA that focus on pharmaceuticals increased from 32% prior to 1990 to 48% from 1990–2005. U.S.-based investigators account for 53.6% of the total (47.5% of pharmaceutical CUA). Significant predictors for using pharmaceutical CUAs were study quality (OR 1.96; 95% CI-1.3–2.5), publication in a high-volume journal (OR 1.85; 95% CI-1.18–2.89), and year of publication. CONCLUSIONS: CUA have been rapidly adopted, especially among UK-based investigators. If CUA turn out to be a useful tool to decision makers, this trend is encouraging, but means to achieve more rapid deployment should be identified.

THE ADOPTION AND DIFFUSION OF COST-EFFECTIVENESS ACCEPTABILITY CURVES IN PUBLISHED ECONOMIC EVALUATIONS

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Cost-effectiveness acceptability curves (CEACs) plot the probability that one treatment is more cost-effective than another, as a function of a societal threshold willingness to pay for additional units of efficacy (e.g., life-year or QALY gained). OBJECTIVES: To assess the adoption and diffusion rates of CEACs within the field of economic evaluations. METHODS: We used the Tufts-New England Medical Center registry of 620 published cost-effectiveness analyses (CEA), presenting an original cost/QALY ratio from 2002-2005 (http://www.tufts-nemc.org/cearegistry/). For each CEA we recorded the year of publication, journal’s name, study origin (country), and a subjective assessment of overall study quality ranging from 1 (low) to 7 (high). We used univariate analyses (chi-square and t-test), to assess differences in CEAC use by year of publication, study origin and quality. We also compared practices in journals publishing a high-volume (n ≥ 10) versus low-volume (n < 10) of CEs during the study period. We used multivariable logistic regression to identify factors predicting CEAC use. RESULTS: Approximately one fifth (20.2%) of CEs presented a CEAC. The adoption of CEACs has increased over time from 5.3% (2002) to 30.4% (2005) (p < 0.0001). Studies using CEAC were of higher quality (4.6 ± 1.0 vs. 4.1 ± 0.9; p < 0.0001) and more prevalent in high-volume journals (30.7% vs. 16.4%; p < 0.0001). CEACs were more frequently used in UK studies (48.8%) versus studies from Sweden (24.1%), The Netherlands (17.9%), United States (11.7%), and Canada (9.1%). Significant predictors for using CEACs were study quality (OR 1.96; 95% CI-1.53–2.5), publication in a high-volume journal (OR 1.85; 95% CI-1.18–2.89), and year of publication. CONCLUSIONS: CEACs have been rapidly adopted, especially among UK-based investigators. If CEACs turn out to be a useful tool to decision makers, this trend is encouraging, but means to achieve more rapid deployment should be identified.
**Abstracts**

**THE $50,000/QALY THRESHOLD RECONSIDERED: A RETROSPECTIVE ON KLARMAN’S ORIGINAL PAPER WITH AN EYE TO THE FUTURE**

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It has been 40 years (1968) since Herbert Klarman and colleagues published their paper in Medical Care establishing that the cost-effectiveness of kidney dialysis is $50,000/QALY. This served as the basis for expanding the United States Medicare program to provide universal coverage for end stage renal disease and subsequently the basis upon which all new health technology has been compared. This standard has not changed throughout the health technology assessment community despite years of inflation and structural changes in health care systems since this time. This paper will first re-examine Klarman’s work and show how quality-adjusted life years in the wrong direction—producing ill-year rather than healthy-year equivalent years; therefore, he grossly underestimates the cost-effectiveness ratio associated with kidney dialysis. The implication of this mistake for health technology assessment and some suggestions for new CE threshold standards will be discussed. Current conditions in health technology assessment require that these new standards be both dynamic—allowing for change over time—and flexible to allow adjustment based on mitigating factors like budget impact. Several examples and evidence from Australia, the UK and the United States will be presented to indicate how these standards might be developed.

**TOTAL DIRECT MEDICAL EXPENDITURE OF CHRONIC DISEASES UNDER DIFFERENT ECONOMETRIC MODELS**

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OBJECTIVE: Quantify effect of alternative econometric models, in estimating total direct medical expenditure in diabetes, arthritic, cardiac diseases, asthma, hypertension, stroke, and emphysema. METHODS: Data from the MEPS’s Household Component (2004), a nationally representative survey of the U.S. civilian noninstitutionalized population, was used. Accounting for the survey’s clusters, strata and sampling weights; total direct medical expenditure was estimated under 11 different econometric models. Models compared were, OLS on raw-expenditure (OLSraw); OLS on log-expenditure (LnHom) and homoskedastic-retransformation; OLS on log-expenditure (LnHet) and heteroskedastic-retransformation; GLM with log-link and Gamma-family (GLMGam); GLM with log-link and Poisson-family (GLMPoi); Extended Estimating Equations (EEE); and 2-part models of OLSraw (2POLSraw); LnHom (2PLnHom); LnHet (2PLnHet); GLMGam (2PGLMGam); and GLMPoi (2PGLMPoi). Incremental expenditure from the method of recycled predictions summed over diseased population gave total expenditure. Box-Cox test confirmed log-link for GLM models while Modified Park’s test determined a distribution between the Poisson and the Gamma for the family. LINK, RESET and Hosmer-Lemeshow test determined model fit, while COPAS test was employed for over-fitting and cross validation. Covariates included age, gender, race, ethnicity, marital status, education, insurance status, and comorbidity. RESULTS: Total expenditure in billions (b) of dollars, for diabetes ranged from $48.5b(2POLSraw) to $127b(LnHet). Similarly, expenditure of arthritis ranged from $73b(2POLSraw) to $196b(LnHet); cardiac diseases ranged from $99.2b(2POLSraw) to $194b(LnHet); asthma ranged from $27.8b(2POLSraw) to $64.2b(GLMGam); emphysema ranged from $2.1b(2PLnHom) to $18.4b(LnHet); hypertension ranged from $69.9b(2POLSraw) to $241b(LnHet) and stroke ranged from $13.1b(2PLnHom) to $39.3b(LnHet). LnHet model was consistently associated with the highest total expenditure estimate, while 2POLSraw model typically predicted the lowest estimate. CONCLUSION: The strong influence of model choice on the total medical expenditure estimate, underscores importance of understanding the data generation procedure before selection of the appropriate estimator.

**A CONCEPTUAL FRAMEWORK TO ANALYZE A DISEASE’S WORKPLACE IMPACT ON AN EMPLOYER**

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OBJECTIVES: A disease’s workplace impact on an employer is often highly sought but rarely available information that an employer can use to understand the value of a health intervention and to influence health insurance coverage of that intervention. This document presents a conceptual framework to analyze a disease’s workplace impact on an employer. METHODS: The conceptual framework presented here was developed on the basis of a comprehensive literature review, extensive consultation process, analytical mapping of concepts, objects, behaviors, domains, functions, and relationships, as well as real case analyses. RESULTS: A four-component conceptual framework of workplace impact of a disease is proposed to guide researchers to quantify disease-workplace-impact from an employer perspective. These four components are work interruption costs, work care costs, worker turnover costs and productivity reduction costs. The examples of work interruption costs include employer-paid medical leaves, absence, short-term disability, and other forms of work interruption resulted from a disease. The examples of work care costs include disease related work adaptation costs, and a disease related insurance premium increase. The examples of worker turnover costs include worker separation costs, new worker recruitment costs, and new worker training costs. The productivity reduction costs are mainly the costs of productivity decrease resulted from presenteeism. Both predisposing factors and intervening factors of workplace impact are discussed in this conceptual framework. Based on this conceptual framework, we conducted a real world case analysis, which suggests not only significant workplace impact of a debilitating disease, but also some methodological challenges in estimating workplace impact of a disease from an employer’s perspective. CONCLUSIONS: Our four-component conceptual framework can guide researchers to quantify workplace impact of a disease from an employer’s perspective. The real case analysis suggests a debilitating disease not only affect patients, but also exert significant workplace impact on an employer.