Phase 3 study examining adjunctive armodafinil for the treatment of a major depressive episode associated with bipolar I disorder (NCT01072929). **METHODS:** To assess the safety and efficacy of adjunctive armodafinil 150 mg/day in a heterogeneous sample of patients, this 8-week, double-blind, placebo-controlled, multicenter study evaluated adult patients with bipolar I disorder who were currently experiencing a major depressive episode while taking 1-2 maintenance therapies (mood stabilizers and/or second-generation antipsychotics). **RESULTS:** The study was conducted at 70 centers in 10 countries from January 2010 to March 2012. Of 786 patients screened, 433 were randomized. Baseline disease severity as assessed by mean (SD) IDS-C_{30} total scores was characteristic of moderate depression (43.6 [6.93] and 43.2 [7.76] for the placebo and 150 mg groups, respectively). The most common concomitant treatments were valproate, lithium, and lamotrigine. Patients in the placebo and armodafinil 150 mg groups experienced their first depressive episode 13.8 (SD 10.24) and 14.5 (SD 11.73) years prior to screening, respectively. The number of distinct regimens of adjunctive treatments will also be reported. **CONCLUSIONS:** Because the design allowed a wider range of adjunctive maintenance therapies, subjects enrolled in this study may be more representative of patients in clinical practice. The diversity of therapeutic regimens encountered in this study may improve external validity/generalizability without sacrificing assay sensitivity, although a large sample size was necessary. Further studies are needed to explore how research on bipolar depression treatments can improve external validity by employing more inclusive designs without sacrificing assay sensitivity.

PRM215

INVESTIGATOR-INITIATED APPROACH TO ADDRESS AN OPTIMIZATION PROBLEM IN DESIGNING COST-EFFICIENT STUDIES

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OBJECTIVES: To improve research productivity in an economic environment with limited resources, researchers may need to consider investigator-initiated approaches to design cost-efficient studies. A cost function was developed to guide decisions about trade-offs to be made in clinical trial design with the objective of minimizing cost while achieving a given level of power to detect differences in patient-reported outcomes. **METHODS:** The design and conduct of a clinical study was treated as a constrained optimization problem. A cost function was developed, a Lagrangian function was constructed, and first-order partial derivatives were taken with respect to each choice variable (e.g., number of recruitment sites, number of follow-up visits, and study duration). Comparative statics analysis was used to examine the changes in the choice variables as a result of changes in the exogenous variables. **RESULTS:** A necessary condition to minimize cost while achieving a given power is the equivalence of the ratios of the marginal cost associated with increasing each choice variable and the marginal change in power associated with each choice variable; in other words the same cost per unit of output created by each input at the margin. For second-order condition, we made the reasonable assumption that increasing the number of participants recruited leads to a decrease in the marginal rate of change in the Type II error which holds. Comparative statics analysis showed that the increase or decrease in the rate of recruitment, expected percent loss to follow-up, and the cost of interventions lead to different trade-offs between the marginal cost of conducting the clinical trial and the marginal change in the probability of committing a Type II error. **CONCLUSIONS:** In light of funding challenges, researchers could consider the trade-offs required to achieve a cost-efficient study for a given level of power using methods from economics and optimization.

PRM216

MULTI-NATIONAL RETROSPECTIVE CHART REVIEW STUDIES: LESSONS LEARNED FROM APPLICATION OF METHODOLOGY TO INTERNATIONAL EVALUATIONS OF BURDEN OF ILLNESS AND DRUG UTILIZATION AND SAFETY

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OBJECTIVES: In the absence of suitable health care databases, chart review studies can result in tailored datasets suitable for evaluations of burden of illness, unmet need and drug utilization and safety. This methodology, however, is associated with significant design and operational challenges. **METHODS:** Design and operational parameters of ten recent chart review studies of treatment patterns, resource utilization and costs of care, clinical outcomes and/or drug utilization and safety conducted in Canada, the United States, and western Europe have been summarized. Opportunities, challenges and lessons learned have been delineated in detail. **RESULTS:** Four of these studies were categorized as post authorization safety studies, and all but one of these studies was mandated by the FDA or EMA. Six of the 10 studies were in oncology, and evaluated outcomes in patients who had failed at least one line of chemotherapy. Sample size varied from 20 patients to greater than 2000, and the number of countries and sites varied from 1-6 and 4 to 375 respectively. Across studies, key challenges included delineation of eligibility and study periods that permit evaluations of recent care patterns yet allow for sufficient follow-up time; design and local implementation of case ascertainment and sampling frame methodologies; and safety reporting in the context of retrospective source data. Drug utilization studies evaluating inappropriate or off-label use required careful attention to protocol language to minimize response bias, as well as a carefully executed operational plan for the identification of prescribers and the collection of data from prescribers over time. **CONCLUSIONS:** Though challenging to implement, retrospective chart reviews are frequently necessary to address research questions spanning burden and costs of care to drug utilization and safety. A series of national and multi-national chart review case studies with diverse research objectives highlight common design and operational challenges that can be anticipated and overcome.

PRM217

TIME AND MOTION STUDY DESIGN: HANDLING VARIABILITY AND CONFOUNDING OF RESULTS

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Time and Motion (T&M) studies quantify time-related outcomes. Any given intervention process can be broken down into a set of pre-defined tasks for repeated observations, allowing estimation of the mean task durations in support of health economic analyses. While aiming to achieve robust estimates, variability in time measurements remains a main methodological challenge. **OBJECTIVES:** To discuss the importance of handling variability and confounding in T&M studies. **METHODS:** Investigation of the impact of variability on process duration begins with the analysis of process flow predictors and particularly the identification of potential confounders of process duration. Process-related variability can result from differences between countries or centers (e.g., geography, institution type) or within centers (e.g., patient characteristics, process specifics). Additional variability in time measurements can be due to insufficient delineation of tasks and inter-rater differences. **RESULTS:** Once potential sources of variability are identified, it must be decided whether a variable is to be minimized or accounted for in the study design relating back to the health economics objective of the T&M study. For instance, clear delineation of processes to be observed and thorough training help limit inter-rater variability. On the other hand, limiting data collection to a homogenous sample of centers and patients (i.e., specific patient and process characteristics), while minimizing variability in study setting and population, can compromise generalizability of the results. In situations where a medical intervention can be used to treat a broad range of patient populations with distinct clinical characteristics, limiting data collection to a certain subgroup means generating results applicable to these patients only. **CONCLUSIONS:** Variability can be controlled through thoughtful study design. However, significant confounders should be identified and accounted for to produce valid process time estimation. Proper handling of variability in time measurement will improve precision of the duration estimates in support of health economic analyses.

RESEARCH ON METHODS – Conceptual Papers

PRM218

THE CHALLENGE OF EVIDENCE SYNTHESIS WITH SPARSE OR RARE EVENTS: HOW BAYES CAN HELP?

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BACKGROUND: With the emergence of systematic reviews for evidence-based evaluations in health care, the quantitative methods to synthesize evidence have been increasingly developed and used to support decision making Particularly in the context of HTA evaluations where both post-marketing and pre-marketing data may be considered, the evidence to be synthesized can be sparse or related to rare outcomes such as risk outcomes. The Bayesian option has increasingly appeared as an unrivalled option for such challenging evidence synthesis cases. **OBJECTIVES:** This work aims at highlighting the strengths and limitations of Bayesian meta-analysis and mixed treatment comparisons and at providing guidance to doers and users of such evidence syntheses in the context of health technology assessment with rare or sparse health outcomes in the real-world setting. **METHODS:** Through a list of case studies in risk or benefit/risk studies and simulation-based comparisons, the state-of-the-art Bayesian meta-analytic approaches are reviewed, adapted to the context of rare events and evaluated for their robustness. Under-reporting of risk outcomes in post-marketing studies is accounted for in the Bayesian models and sensitivity to the choice of priors is analyzed. **RESULTS:** Provided thorough validation procedures and careful model and prior calibration, the Bayesian framework offers an unrivalled framework for evidence synthesis of scarce data, for both direct and indirect comparisons, with fair and robust quantification of uncertainty. **CONCLUSION:** Guidance can be derived based on the nature and quantity of data which do impact the methods reliability, in order to help practitioners and decision makers in using Bayesian meta-analysis and models for scarce data in various country and decision settings.

PRM219

THE VALUE OF A GOOD DECISION: ASSESSING THE ECONOMIC BENEFITS OF DECISION AIDS

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Decision aids are increasingly used to support doctors and patients in shared health care decision making, yet methods to measure their benefits for economic evaluation have received limited attention. Significant non-health benefits such as improved patient knowledge, experience and satisfaction may accrue through the use of decision aids. These cannot be assessed within the dominant health economic framework of cost utility analysis. The objective of this paper is to propose a new opportunity cost-based method suitable for assessing the benefits of decision aids relative to other interventions in a resource-constrained health care system. A literature review to identify how decision aids have been evaluated found that economic evaluations are limited. Non-health benefits