Phase 3 study examining adjunctive armodafinil for the treatment of a major depressive episode associated with bipolar I disorder (NCT01772929). 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 (one 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 total score 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 group experienced their first depressive episode 19.8 (SD 10.24) and 14.5 (SD 11.73) years prior to screening, respectively. The number of distinct regions of adjudicate treatments will also be reported. CONCLUSIONS: Because the design allowed for recruitment 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

Huang M1,2, Clark M1,2, Fiatarone M1,2
1Analysis Group, Boston, MA, USA, 2Brown University, Providence, RI, USA, *Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

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 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 conditions, 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 in outcomes in patients who had failed at least one line of chemotherapy. 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

Eagor K1, Stein D1, Sternhagen A1
1United BioSource Corporation, Dorval, QC, Canada, 2United BioSource Corporation, Blue Bell, PA, USA

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 were conducted in Canada, the United States, and western Europe have been summarized. Opportunities, challenges and lessons learned have been reported 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 1140 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 575 respectively. Across studies, data collection included delineation of methodology 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, including delineation of strategies to measure these benefits from economic analyses, 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. 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
have been measured with knowledge and satisfaction questionnaires, but have not been assessed within a choice-based methodology. The key function of a decision aid is to provide information for a patient to make an informed decision and to replace activity within the healthcare system (the opportunity cost) would be physician consultation time. We propose a stated preference consultation time trade-off (CTTO) in which a proportion of a hypothetical 10-minute physician consultation time is traded for use of the decision aid by a patient with prior experience of the aid. Conceptually, a patient is trading a substitute source of health care information to maximise their utility of the consultation experience. The CTTO may be reported in consultation minutes or converted to a monetary value using the local cost of physician time. These values can be used alongside the cost of the decision aid, for economic evaluation. The CTTO is currently being evaluated within a clinical trial of a cataract decision support tool.

PRM220 DIRECT-TO-PATIENT STUDY DESIGNS FOR PHARMACOVIGILANCE de Mair C, Michel P, Wiederkehr S1, Jones M, Fournie X1
1REGISTRAT-MAPI, Lyon, France
Post-marketing non-interventional safety studies typically enroll patients at sites where patients receive care. During patient follow-up the occurrence of safety events of interest is recorded by site personnel based on information obtained from the patient during standard-of-care visits. Although this is the traditional approach for assessing the occurrence of safety events in the post marketing setting, it has several practical shortcomings, including high cost associated with site start up, management, and data collection; infrequent or irregular standard-of-care visits; patients switching health care providers; transient nature of adverse events; treatment at multiple sites, and at non-sites, and the cost of seeking the safety events. A design alternative that overcomes several of these shortcomings includes direct-to-patient contact and follow-up. In this approach, enrolled patients are regularly contacted via phone during follow-up and the occurrence of adverse events is reported by patients without potential signal and symptoms associated with the safety events. If either is reported by the patient, trained personnel follow up with the patient’s treating physician for further evaluation through phone interview and/or written confirmation of the safety event. We will present three examples of studies that make use of this direct-to-patient approach to capturing safety data. These studies comprise large multi-national and national studies with sample sizes ranging between 2000 to over 10,000 patients. In one study, the safety events include thromboembolic and bleeding events in patients discharged from hospitalization for acute coronary syndrome. In two others, safety events comprise anaphylaxis, except Bell’s palsy, neuritis, etc. associated with influenza vaccines. For each study, we will present specific design characteristics; procedures for patient contact, follow-up, and interviews; and procedures for confirming the occurrence of safety events. Strengths and weaknesses of the direct-to-patient approach will be discussed and recommendations regarding appropriate indications and safety events best suited to this novel methodology will be presented.

PRM221 MPR AND PDC: IMPLICATIONS FOR INTERPRETATION OF ADHERENCE RESEARCH RESULTS Clancy ZA
Jefferson School of Population Health, Philadelphia, PA, USA
OBJECTIVES: To compare and contrast the Medication Possession Ratio (MPR) and treatment duration covered (PDC) metrics of adherence, and 2) to understand the implications of measure choice and specific definition on study results.

METHODS: Two adherence measures, MPR and PDC, were selected for comparison. We will present the data from our previous research examining patient compliance in the claims data set and literature. To highlight the effect of measure selection, examples demonstrating contrasting results for MPR and PDC are presented. Furthermore, the impact of numerator and denominator specification within each of those measures is examined and illustrated with examples. Implications for assessing and interpreting published research studies are presented.

RESULTS: Although MPR and PDC have been operationally defined in similar ways in the literature, there are differences that could yield distinct results. The basic structure of these measures is a ratio with a proxy for the number of compliant days in the numerator and the number of days in a measurement period in the denominator. MPR is based on the sum of dispensed ‘days supply’ over the measurement period, whereas PDC is based on evaluation of available supply for each day. MPR is based on the sum of dispensed ‘days supply’ over the numerator and the number of days in a measurement period in

v vary substantially between countries. Quantification of opioid-dependence treatment costs could help to optimise health policy decision-making regarding treatment provision. A health economic (HE) model was developed to calculate the costs associated with different treatment modalities in Europe allowing for comparison of different treatment systems. Total costs incurred, on a per-patient and national level, were calculated. A literature review was undertaken to establish current evidence on all aspects of opioid treatment and opioid dependence. The HE model assesses direct costs (including medications, supervision and dispensing, staff costs, testing costs, other health care costs and miscellaneous costs) associated with the model of treatment in place in each country, local according to national guidelines, and allows for comparison of the costs associated with different medication options. Local cost data were sourced by health economics groups in each of the relevant countries, and were drawn from publicly available databases and published literature where possible. Expert opinion was used to fill in any remaining data gaps. Seven countries were included in the analysis with the initial focus being Belgium, France, Germany, Italy, Portugal, Spain and UK. The primary output of the HE model, which will be presented, is the total per-patient cost of providing treatment for opioid dependence in each country. The HE model also provides the total cost of each treatment model in each country. Outputs are being validated against publicly available statistics on the total number of patients treated and the total cost to treat them, in each country. This HE model provides a tool to support discussions on and implementation of cost-effective models of care for opioid dependence around Europe.

PRM223 IMPLEMENTATION OF PATIENT-REPORTED OUTCOMES ASSESSMENT IN A POST MARKETING SAFETY SURVEILLANCE: PARALLELS IN JAPAN AND GLOBAL PLANNING Adachi K1, Migita H2, Yamanaka S1, Wang ECY1, Rossi B1
1Bayer Yakuhin, Ltd., Tokyo, Japan, 2Bayer Yakuhin, Ltd., Osaka, Japan
The PMS plan of PRO assessment results to stakeholders, such as physicians and patient organizations. We will discuss above issues associated with a PRO survey as a part of PMS from both Pharmacovigilance and Outcomes Research points of view based on our experience in Japan. A comparison will also be made about study planning with a PMS component between Japan and global PMS (such as the Post-Authorization Surveillance required by the European Medicines Agency), to highlight differences and similarities. Furthermore, to provide RSs with guidance on PRO use for post marketing safety surveillance, we will highlight how researchers and practitioners to enhance the usage of PMS as a valuable opportunity to obtain real-world PRO assessments.

PRM224 ELECTRONIC PATIENT REPORTED OUTCOMES (ePRO): THE BEST DEFENSE IN PREVENTING MISSING PRO DATA Ross J, Ross E, Holzbaur F
Almac Clinical Technologies, Sauderton, PA, USA
This session will illustrate how ePRO is a powerful approach for preventing missing data; explain how ePRO techniques can be implemented to prevent missing data. ePRO use can be an effective solution for preventing missing data as compared to paper data collection. Missing data is common in PROs and can result in significant problems for data analysis. While using a robust statistical plan for handling missing data is beneficial, studies still can suffer with high levels of missing data. One major contributing factor is the collection method. Many PROs are still administered in a traditional paper format which can result in high levels of missing data. This presentation will illustrate how ePRO can prevent missing data through providing examples of various ePRO techniques that can be implemented. Primary ePRO techniques to minimize missing data include: hard core, skip patterns to eliminate patients skipping testing items or pages; reminders with real-time technology to remind patients to complete their PROs; alerts to study staff of patient non-compliance, programmed logic to reduce erroneous entries among reporting responses, and a missing data correction plan that is completed within the given window; and storage of directly entered data with back-up can ensure data is not lost. ePRO can prevent missing data, improve patient compliance and result overall in high quality data. ePRO eliminates many of the issues associated with traditional PRO instruments. Future PRO development efforts should focus on creating more electronic versions of PRO instruments. Wider availability of ePRO instruments across different treatment settings would ultimately result in high quality data and reduced missing data.