RESEARCH ON METHODS – Study Design

PRM209
HOW ARE CENTRES INCLUDED IN RANDOMISED CONTROLLED TRIALS WITH PARALLEL ECONOMIC EVALUATIONS IN THE UK?

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OBJECTIVES: The sample of centres participating in randomised controlled trials (RCTs) may affect the generalisability of economic evaluation results if it is biased, but there is limited evidence on how trialists currently include centres in RCTs. Our aim was to investigate the reported rationales for centre selection in RCTs with parallel economic evaluations in the UK. **METHODS:** We systematically reviewed and meta-summarised centre selection information in full-length protocols of RCTs with parallel economic evaluations funded by the UK National Institute of Health Research – Health Technology Assessment programme (NIHR-HTA) and initiated between January 2005 and January 2012. Free text information on centre selection was extracted, abstracted and categorised; effect sizes (%) were calculated for the emerging categories as a measure of prevalence relative to the number of included studies. **RESULTS:** Of 365 reviewed studies, 129 trial protocols were included in the systematic review with a total target sample size of 317,000 participants. The meta-summary identified 53 centre selection considerations, grouped under three categories: diversity and representativeness, centre characteristics and trial participation. A total of 78 (60%) protocols provided a rationale for centre selection. A total of 31 (24%) protocols explicitly considered representativeness, for example in terms of the target population (11%) and delivered services (12%). Fifty-seven (44%) protocols required particular centre characteristics, such as size (17%) and research experience (15%). Thirty-seven (29%) protocols envisaged considerations that would ensure successful trial participation, such as the willingness to participate (7%) and ensuring recruitment (13%). **CONCLUSIONS:** The rationale for centre selection in RCTs with parallel economic evaluations is currently underreported in trial protocols. Centres are primarily enrolled on pragmatic grounds and less so with a view to ensuring generalisability. There are little reasons to believe that economic results from RCTs are informed by a representative sample of centres, thus questioning the representativeness of their findings.

PRM210
RECRUITING PATIENTS WITH A RARE BLOOD DISORDER AND THEIR CAREGIVERS THROUGH SOCIAL MEDIA

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OBJECTIVES: Recruiting research participants with experiences relevant to rare diseases (patients and caregivers) remains a constant challenge. Researchers often rely on patient advocacy or support groups as well as clinician referrals, which each present unique recruitment issues. Social media sites, such as Facebook, can potentially be helpful in recruiting patients for many study types, particularly those involving hard-to-reach populations. However, little is known about the value of social media in recruiting populations with rare medical conditions. In this study, Facebook was used to recruit adult patients and parents of children with hemophilia A for participation in a Web-based survey. **METHODS:** A cross-sectional study was developed to better understand patient and caregiver experiences and behaviors associated with treatments for hemophilia A. Members of three local or national blood disorder organizations in the United States and Canada were invited to complete a Web-based survey via postings on each organizations' Web site and/or e-mail invitations sent to each organizations' member lists. Additionally, two organizations posted advertisements about the study on their respective Facebook pages. A nominal donation was made to each organization for their assistance in study recruitment. **RESULTS:** Of the 145 individuals who responded to survey invitations, 101 (70%) completed the survey questionnaire. More than half (58%) of the completed questionnaires were from respondents recruited through Facebook who were a mean age of 35.8 years (SD = 8.3), similar to those recruited through more standard methods. The organization that did not post a study advertisement on Facebook recruited the fewest participants (only 13% of the total respondents). **CONCLUSIONS:** This real-world study emphasizes the assistance and value of social media in study recruitment. Use of social media in recruiting can be an efficient means of reaching large numbers of potential respondents.

PRM211
THE EFFECTS OF EXCLUDING TREATMENTS FROM NETWORK META-ANALYSIS

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OBJECTIVES: To investigate the effect of omitting treatments from network meta-analyses on overall treatment effects and treatment rankings. **METHODS:** We selected published network meta-analyses that met the following criteria: compared t≥5 treatments, had ≥2 loops, ≥2tstudies and set to determine treatment superiority. If multiple published analyses considered the same treatments (e.g. multiple networks pertaining to COPD drugs), the larger network was selected. We defined a node's connectivity as its number of edges. Each network was analyzed systematically with the removal of one node at a time. Nodes that were in ≥50% of studies were not removed. Impact of node exclusion was measured using the relative change in treatment effect estimates, changes in the top-three ranked treatments, and changes in probabilities of being the best treatment. Relative changes in effect size were expressed as fold-deviations. For each network with excluded node(s), we measured the maximum and geometric mean of fold-changes. **RESULTS:** In total, 19 networks were selected for analysis. Approximately half the networks had average fold-change larger than 1.10 (greater than 10% relative change in treatment effects). Approximately half of the networks also had changes in the top three ranks and substantial changes in treatment rank probabilities. Within these networks, the maximum fold-change was generally larger than 1.25. In networks with no changes in top-three ranked treatments, the 'best' treatment mostly had probability ≥70% of being the best. Two features were consistent across the nodes leading to the largest change in probabilities and effects: they were among the most connected nodes and tended to have a 0% probability of being the best treatment. **CONCLUSIONS:** Network meta-analytic methods are still in their infancy. Our results suggest that failing to include one or more treatments within a network can lead to important changes in conclusions reached.

PRM212
USING AN ONLINE DATA ANALYTIC TOOL TO INFORM STUDY DESIGNS FOR CHRONIC DISEASE POPULATIONS: A CASE STUDY WITH CLL

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OBJECTIVES: Chronic lymphocytic leukemia (CLL) accounts for almost 40% of all leukemias. Current treatments have high rates of adverse events requiring hospitalization. With promising treatments on the horizon, the need for well-designed studies of treatment patterns and adverse events will increase. Designing studies can be challenging given the long-term nature of CLL. This study uses an online analytic tool to explore the necessary observation period to accurately assess treatment and hospitalization rates. **METHODS:** Using the Treatment Pathways tool and data from an 8-year oncology subset of the 2004 – 2012 MarketScan®databases, we identified patients with two plus claims for CLL, one year prior enrollment, no prior treatment. Four follow-up groups were assessed: 1, 2, 3, and 4 years of continuous enrollment (CE). For each CE, we identified patients treated with bendamustine (B), or fludarabine, rituximab, and/or cyclophosphamide (F/R/C). Treatment and hospitalization rates and the time between diagnosis, treatment, and hospitalization were calculated. **RESULTS:** A total of 4886 patients met all inclusion criteria; 3348 had 1 year, 2201 had 2 years, 1451 had 3 years, and 874 had 4 years CE. Bendamustine use increased from 4% among those with 1 year CE to 5% for all other CE groups. F/R/C use increased from 21% among those with 1 year to 27% among those with 4 years CE. Hospitalization rates increased from 41% to 49% for bendamustine, and 38% to 44% for F/C/R from 1 year to 4 years CE. Among those with 4 yrs CE, median time to first treatment was 4.3 years for bendamustine, 1.4 years for F/C/R; median time to first hospitalization was 96 and 365 days, respectively. **CONCLUSIONS:** This study used an online tool to quickly assess the impact of various CE criteria. The data demonstrate how shorter CE underestimates treatment, related hospitalizations, and overall burden of illness in a chronic population.

PRM213
USING REAL-WORLD CLAIMS DATA FOR PLANNING ONCOLOGY CLINICAL TRIALS

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OBJECTIVES: To understand the value of quickly estimating the impact of certain inclusion/exclusion criteria on a potential clinical trial population using real-world administrative data. **METHODS:** Using the Treatment Pathways tool and data from an 8-year oncology subset of the 2004 – 2012 MarketScan®databases, we identified patients with castrate-resistant prostate cancer (CRPC) with at least six months of history. From these patients, we identified cohorts with definitive exclusions (brain metastasis or other primary cancer) and time-dependent exclusions (based on radiation or treatments). Seven of 12 exclusion criteria were identifiable within the claims database. **RESULTS:** Inclusion criteria identified 2,329 patients with CRPC based on two prostate cancer diagnoses, medical or surgical castration and receipt of docetaxel. Of them, 1370 (59%) had 6 months of follow-up data for evaluation of exclusion criteria. Among the 1370 patients, 248 (18%) met none of the exclusion criteria, while 482 patients (35%) had brain metastasis and/or other cancers. The remaining 640 (47%) had at least one time-dependent exclusion, including 534 receiving corticosteroids, 136 receiving androgen receptor and reductase inhibitors, 86 receiving radiation and 31 with ketoconazole. These patients could be trial-eligible depending on the timing of treatment cessation and trial recruitment. **CONCLUSIONS:** This study demonstrates a method to understand the impact of specific inclusion/exclusion criteria on a potential clinical trial population in just a few hours using an online pathway creation tool and administrative data representing millions of patients. Using this method, trial planners can evaluate different scenarios to quickly and easily determine estimated attrition rates helping them to maximize potential recruitment success. Limitations exist due to the timing of exclusions and data on lab results included in the exclusion criteria that were unavailable in this subset of claims data.

PRM214
USE OF A NOVEL ADJUNCTIVE CLINICAL TRIAL DESIGN TO EXAMINE EFFICACY, SAFETY OF ARMODAFINIL FOR THE TREATMENT OF BIPOLAR I DEPRESSION

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OBJECTIVES: Patients in randomized, controlled trials of bipolar depression are generally not representative of a clinical population. This study attempted to examine a large sample of patients more representative of patients seen in clinical practice. This report presents baseline patient characteristics from a

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