both challenges and opportunities for industry. The changes in the DSM-5 criteria may translate into changes for how we go about developing medical products to treat psychiatric disorders, including ADHD. There will need to be an investment in research and education, and sponsors must examine the possibility of developing new endpoints and outcome assessments for use in clinical trials.

PMR185 THE IMPACT OF DSM-5 ON THE DEVELOPMENT OF DRUGS TO TREAT MAJOR DEPRESSIVE DISORDER

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OBJECTIVES: In May 2013, the American Psychiatric Association released the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a classification system for psychiatric conditions. DSM-5 brings significant changes to many diagnostic categories as compared to the previous edition. The objective of this review is to examine the changes that may be expected in future submissions to the NMA of the new DSM-5 criteria and discuss the impact these changes may have for industry. METHODS: A line-by-line review of the DSM-5 and DSM-IV criteria for MDD was undertaken. Significant changes were highlighted and discussed from the point of view of sponsors of new submissions to the NMA. RESULTS: The primary symptom criterion for MDD remains unchanged, requiring five of nine symptoms, over a two-week period. The changes of note have to do with the differential diagnoses and specifiers. One change that received significant attention in the time leading up to the publication of DSM-5 was the elimination of the bereavement exclusion, which discounted bereavement after the loss a loved one within the first two months as part of the normal grief process. In terms of pretications, a new addition in MDD is “with anxious distress,” referring to episodes of depression characterized by at least two of five symptoms of anxiety. DSM-5 notes that this is associated with “greater likelihood of treatment nonresponse”. Preferred factor sponsors may wish to consider in developing their trial inclusion/exclusion criteria. CONCLUSIONS: The significant changes in DSM-5 pose both challenges and opportunities for industry. The changes in the DSM-5 criteria translate into changes for how we go about developing medical products to treat psychiatric disorders, including MDD. There will need to be an investment in research and education, and sponsors must examine the possibility of developing new endpoints and outcome assessments for use in clinical trials.

PMR186 PATIENT NETWORKS AS A DATA SOURCE FOR PATIENT REPORTED OUTCOMES

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OBJECTIVES: To explore the potential of online patient networks (PN) as a viable source of PRO data for clinical research. Several have emerged in the last few years in different European countries, and as a natural meeting point for chronic patients with an active engaged with their communities, they represent a promising source of patient reported data. In this original, the experience with the French PN “Carenity” is described. METHODS: Given the great heterogeneity of the users of “Carenity”, and the fact that the test was computer-led by definition, a Computer Adaptive Test (CAT) was considered the best choice. The authors decided to use a culturally adapted version of CAT Health system, which measures generic health-related quality of life (HRQoL). However, in absence of a calibration for the French PN seems to be a fast way to obtain PRO scores directly from patients. Preliminary results: 243 separate interventions were analysed to seek common themes; and assess how often any one type of criticism was associated with a rejection by NICE. RESULTS: A total of 181 NICE technology appraisal reports were evaluated. These covered 243 separate interventions, 83 (34%) of which were drugs for cancer. Overall 37-64% of submissions cited NMA, of which 43-83% were criticised, with this proportion having increased over time. Avoidable criticisms related to flaws in the systematic review methodology used to identify relevant RCTs for the analysis, inappropriate pooling of data from heterogeneous studies, and use of suboptimal statistical approaches in conducting the NMA. Unavoidable criticisms related to the lack of RCTs available for competitor drugs in the same indication. However, no association was found between flaws in the NMA and a decision by NICE not to approve the use of the intervention. Instead, such rejection was associated mainly with a lack of evidence of clinical effectiveness in the target populations. CONCLUSIONS: Most criticisms of NMA could be avoided by a more rigorous and transparent approach to conducting and reporting the underlying systematic review and statistical analysis. However, rejection of submissions remains a considerable risk where the underlying evidence is weak.

PMR190 USE OF MULTIVARIATE BAYESIAN EVIDENCE SYNTHESIS TO REDUCE UNCERTAINTY AROUND CLINICAL EFFECTIVENESS AND QUALITY OF LIFE ESTIMATES

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OBJECTIVES: In health technology assessment, decisions about reimbursement of new health technologies are largely based on effectiveness estimates. These estimates are generally provided in the form of RCTs, using patient-reported outcome (PRO) measures. However, sometimes also used to predict the health-related quality of life outcomes, such as EQ-5D, as part of economic evaluation. However, sometimes these effectiveness estimates are not readily available. When many alternative instruments measuring these outcomes are being used (and are not all reported) as part of RCTs, then additional methods are needed to account for this heterogeneity and any uncertainty around the effectiveness. Bayesian multivariate meta-analysis

matrix of likely sample size based on these values ranged from 44 to 193 per group. Based on this DFP, a sample of 120 per group was selected as the sample size that would deliver clinically meaningful results. CONCLUSIONS: A DFP is useful in late phase research to define appropriate sample size where no data exist. It is important to note that DFP methods do not require significance testing, but the benefit is no need for a correction for multiple comparisons at the time of the final analysis.

PMR188 NETWORK CONNECTIONS: CAN CRITICISMS OF NETWORK META-ANALYSIS IN NICE SUBMISSIONS BE AVOIDED?

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OBJECTIVES: To assess 1) how network meta-analyses (NMAs) included within manufacturer submissions to the National Institute for Health and Care Excellence (NICE) have been criticised by its Evidence Review Groups (ERGs); 2) how some of these criticisms might be avoided; 3) the extent to which avoidance might increase the likelihood of a new intervention being approved. METHODS: We reviewed the ERG reports of all NICE technology appraisals published since January 2007 to identify those where the manufacturer’s submission included NMAs. We compared all submissions to the NMA of the drug under assessment. RESULTS: A total of 181 NICE technology appraisal reports were evaluated. These covered 243 separate interventions, 83 (34%) of which were drugs for cancer. Overall 37-64% of submissions cited NMA, of which 43-83% were criticised, with this proportion having increased over time. Avoidable criticisms related to flaws in the systematic review methodology used to identify relevant RCTs for the analysis, inappropriate pooling of data from heterogeneous studies, and use of suboptimal statistical approaches in conducting the NMA. Unavoidable criticisms related to the lack of RCTs available for competitor drugs in the same indication. However, no association was found between flaws in the NMA and a decision by NICE not to approve the use of the intervention. Instead, such rejection was associated mainly with a lack of evidence of clinical effectiveness in the target populations. CONCLUSIONS: Most criticisms of NMA could be avoided by a more rigorous and transparent approach to conducting and reporting the underlying systematic review and statistical analysis. However, rejection of submissions remains a considerable risk where the underlying evidence is weak.

PMR189 METHODOLOGICAL CHALLENGES IN COMPARING TOPICAL THERAPIES IN DERMATOLOGY IN THE ABSENCE OF HEAD TO HEAD STUDIES

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OBJECTIVES: German HTA agency requires evidence about the additional benefit of a new pharmaceutical versus an appropriate comparator as basis for price negotiations. This is challenging when head-to-head studies (H2HS) or randomized placebo-controlled trials (RCTs) are missing and particularly in dermatology, where topical therapies in registration trials are usually compared to their individual vehicle. The aim of this study was to describe different approaches to assess the additional benefit of the test drug. We reviewed methodological aspects in NMa of different topical therapies. METHODS: To assess 1) how network meta-analyses (NMAs) included within manufacturer submissions to the National Institute for Health and Care Excellence (NICE) have been criticised by its Evidence Review Groups (ERGs); 2) how some of these criticisms might be avoided; 3) the extent to which avoidance might increase the likelihood of a new intervention being approved. METHODS: We reviewed the ERG reports of all NICE technology appraisals published since January 2007 to identify those where the manufacturer’s submission included NMAs. We compared all submissions to the NMA of the drug under assessment. RESULTS: A total of 181 NICE technology appraisal reports were evaluated. These covered 243 separate interventions, 83 (34%) of which were drugs for cancer. Overall 37-64% of submissions cited NMA, of which 43-83% were criticised, with this proportion having increased over time. Avoidable criticisms related to flaws in the systematic review methodology used to identify relevant RCTs for the analysis, inappropriate pooling of data from heterogeneous studies, and use of suboptimal statistical approaches in conducting the NMA. Unavoidable criticisms related to the lack of RCTs available for competitor drugs in the same indication. However, no association was found between flaws in the NMA and a decision by NICE not to approve the use of the intervention. Instead, such rejection was associated mainly with a lack of evidence of clinical effectiveness in the target populations. CONCLUSIONS: Most criticisms of NMA could be avoided by a more rigorous and transparent approach to conducting and reporting the underlying systematic review and statistical analysis. However, rejection of submissions remains a considerable risk where the underlying evidence is weak.

PMR187 DEFINING THE PROPER METHODOLOGY TO USE IN A DATA-PEEK FOR POWER (DPF)

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OBJECTIVES: Late phase research is conducted outside the RCT setting where there is uncertainty as to how many subjects are needed to find differences between groups. Due to the lack of real-world information (non-RCT) in late phase designs, there are no tangible inputs for power calculations. This research defines a bias-free methodology that can be used while determining the number of patients in the application of a DPF, a study examining the decrease of HbA1c values in two different insulin delivery methods was examined in patients with several comorbidities. Literature examination found little to no data and a DPF was used to determine effect size (ES) and standard deviations (SDs) once 30 patients had been enrolled in each group. The DPF procedure was: 1) Determine the test statistic; 2) Identify the power formula most appropriate to the test statistic; 3) Determine the v, values used; 4) Follow-up calculations needed for a formula to generate v, 5) Construct a matrix of possible sample size values; and 5) Select a sample size that is obtainable and answers the research question. RESULTS: Data for group A demonstrated a mean reduction of 2.75% ±0.760. group B mean reduction of 3.01% ±0.636. Exact power analysis showed 115 subjects per group would be needed. A
methods have been developed for synthesis of diverse sources of evidence: multiple outcomes, especially outcomes potentially originating from different methodological evidence. These methods were applied to an example in rheumatoid arthritis where outcomes such as the Health Assessment Questionnaire (HAQ), the Disease Activity Score (DAS-28) and the American College of Rheumatology (ACR20) are synthesized. External information about correlations between the outcomes was included in the form of informative prior distributions. Estimates of HAQ were then mapped onto EQ-SD. Also in an alternative approach, the multivariate framework was applied to jointly the utility estimates and the clinical effect outcomes. RESULTS: The use of multivariate meta-analysis led to reduced uncertainty around the effectiveness and utility estimates. Combining the HAQ with DAS-28 gave a 19% reduction in the uncertainty around the estimate of HAQ and also 16% around the estimate of EQ-SD. CONCLUSIONS: By allowing all relevant evidence to be incorporated in economic evaluations of new health technologies, this multivariate approach to meta-analysis can lead to reduced uncertainty and hence more efficient decision-making in health care.

PRM191 NETWORK META-ANALYSIS OF MULTIPLE OUTCOMES: A SIMULATION STUDY AND APPLICATION

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The usefulness of a multivariate approach to compare treatments in the context of pairwise meta-analysis has been widely demonstrated in the literature. However, this approach has not yet been considered for multiple comparisons. We believe that extending such methodology to network meta-analysis (NMA) will improve the precision of relative difference estimates and reduce risk of outcome monotonicity bias. OBJECTIVES: To extend standard NMA to incorporate multiple outcomes of interest and evaluate the use of multivariate NMA models through simulated and real data. We also develop a random multivariate NMA model to account for the correlation between multiple outcome measures. The potential benefits of this method were demonstrated in a simulated example comparing uni- variate and bivariate NMA for continuous outcome measures. We further explored the application of bivariate NMA models in a case study to assess the effectiveness of obesity pharmacological interventions for waist circumference, weight change and BMI change from baseline. RESULTS: The simulation study showed that through the use of multivariate NMA the precision in relative treatment effects was increased when compared to a standard univariate NMA. This held true across all scenarios testing model parameters including both within- and between-outcome correlations. Similar findings were obtained from the application to the example data set in the case study. CONCLUSIONS: Our method proves particularly useful in reducing uncertainty around relative effectiveness estimates when the outcomes included for analysis are highly correlated. However, the advantages of the multivariate NMA are limited where there is little correlation between outcome measures. Further work will explore the applicability of multivariate NMA methods to different types of outcomes such as binary outcome measures.

PRM192 HANDLING VARIABILITY IN TIME ENDPOINTS IN MULTI-CENTRE TIME AND MOTION (T&M) STUDIES: A CASE STUDY OF ERHYTHROPOIESIS-STIMULATING AGENTS FOR ANEMIA MANAGEMENT IN ITALY

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OBJECTIVES: In multi-centre Time and Motion (T&M) studies, time endpoints can be highly variable due to differences in centres practice. Our aim was to assess the impact of the type of analysis employed on the results of a T&M study. METHODS: Data from 13 centres were analyzed with respect to each of the following: drug preparation, distribution, injection, and testing model parameters including both within- and between-outcome correlations. Similar findings were obtained from the application to the example data set in the case study. CONCLUSIONS: Our method proves particularly useful in reducing uncertainty around relative effectiveness estimates when the outcomes included for analysis are highly correlated. However, the advantages of the multivariate NMA are limited where there is little correlation between outcome measures. Further work will explore the applicability of multivariate NMA methods to different types of outcomes such as binary outcome measures.

PRM193 BAYESIAN NETWORK META-ANALYSIS TO ASSESS RELATIVE EFFICACY AND SAFETY OF CANFILGLOFIZIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS (T2DM) INADEQUATELY CONTROLLED WITH METFORMIN

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OBJECTIVES: To assess the relative efficacy and safety of canfilglofizin (CANA), a sodium-glucose co-transporter 2 (SGLT2) inhibitor, as add-on to metformin in adults with prediabetes, compared to other oral antidiabetic agents. METHODS: Bayesian network meta-analysis was conducted based on a systematic literature review described previously. The between-centre (BC) weight for each network was based on treatment- and dose-specific nodes where possible. Non-informative priors were used; selection of fixed versus random-effect model was based on DIC. Studies causing inconsistency (identified through the comparison of direct and indirect evidence) were identified with a clinical expert and excluded from the base case. RESULTS: 25/177 studies reported results at 26/52/104 weeks (w) respectively. HbA1c reduction (2) at 26w/52w was best for exenatide 2mg and liraglutide 1.8mg CANA 300mg and 100mg ranked higher versus DPP-4 (6=0.11 to 0.39) and dapa- (6=-0.12 to 0.38) across all time points; while CANA 100mg conferred at least as large reductions (6=0.1 to 0.3 and 0.00 to 0.26 respectively). The analysis at 104w was conducted based on the pooling of SUs. CANA 300mg and 100mg ranked first/second before liraglutide 1.8mg (6=0.11/0.13 and 0.02/0.04 respectively). Both CANA doses had higher weight-reductions than SU, DDP-4s and pioglitazone, and provided reductions comparable to GLP-1s and pioglitazone. Odds ratios for hypoglycaemia versus SU range from 0.03 to 0.11 for DPP-4 and SGLT. CONCLUSIONS: Add-on therapies to metformin suggests that CANA 300mg is associated with increased HbA1c reduction versus DPP-4 and dapagliflozin while CANA 100mg provides at least similar effects. Additionally, results suggest increasing relative efficacies of CANA over time versus liraglutide and CANA reached at least as large HbA1c reductions as liraglutide at 104w. Weight reduction was comparable to GLP-1s and substantially higher than all other classes. All classes showed significantly less risk of hypoglycaemia compared to SU.

PRM194 ESTIMATING CHRONIC DISEASE PREVALENCE FROM CLAIMS DATA: REDUCING BIAS ACCOUNTING FOR DISEASED INDIVIDUALS WHO DO NOT GENERATE CLAIMS

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OBJECTIVES: Claims data are often used to estimate the prevalence of chronic diseases, typically by dividing the number of patients with disease-related claims (e.g., ≥2 or ≥3 claims) by the number of studied individuals. Such estimates will have a downward bias because not all diseased patients will generate disease-related claims within their enrollment period. This downward bias can be substantial for underserved diseases that lack effective treatments. We explored whether the empirical Bayes methods that were applied to estimate prevalence did not generate claims could improve the accuracy of claims-based prevalence estimates. METHODS: As an example, we studied the prevalence of a rare dermatological condition without any FDA-approved therapies. After accounting for enrollment time, individuals in a nation-wide claims database were identified as having 0, 1, 2, 3, etc., disease-related claims. These counts were modeled using a negative binomial distribution, with an unknown mixing distribution. Empirical Bayes approaches, which are frequently used to estimate numbers of unobserved species in ecological experiments, were used to estimate the number of diseased individuals without claims, and to provide adjusted prevalence estimates. RESULTS: Out of 27 million individuals, at least one year one million, n=2,026 had disease-related claims, comprised of n=1,422 with one claim, n=317 with two claims, n=134 with 3 claims, etc. The traditional method for estimating prevalence identified 4.9 cases per 10,000 persons. After applying the empirical Bayes approach, the estimated prevalence increased to 7 cases per 10,000 persons, and became closer to published prevalence estimates based on non-claims data sources. CONCLUSIONS: In this example application, prevalence estimates based on claims data were increased by 60% relative to using empirical Bayes approaches to account for large numbers of diseased individuals who did not generate claims. The increased prevalence estimates were more consistent with the published literature.

PRM195 APPLICATION OF COPULAS IN ECONOMIC EVALUATION

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OBJECTIVES: To assess the applicability of copulas in distribution in economic evaluation and determine if it is feasible to conduct an analysis of studies of patients with allergic rhinitis in Spain (n=498). Main data were direct cost (€2012) and Health Related Quality of Life (SF-12). We have calculated the goodness of fit for copulas (Gumbel copula, Clayton copula, Frank copula, Normal copula, Plackett copula and T copula) based on the empirical process comparing the empirical copula with a parametric estimate of the copula derived under the null hypothesis. We have used inversion of Kendall’s tau method to fit copulas. A multivariate independence copula was generated based on copulas with c that had been regressed by a 100 times to obtain p-values by bootstrap method. RESULTS: Marginal distribution of direct cost was a 3-parameter Gamma distribution (shape=1.856, scale=6104, location=10.95) in 90% of cases. Kendall’s tau for Health Related Quality of Life was associated to a 1 - gamma (shape=2.9253 and scale=0.1604). P-value range were 0.093 to 0.144 for independent distribution, 0.004 to 0.031 for Gumbel copula, 0.246 to 0.522 for Clayton copula, 0.545 to 0.814 for Frank copula, 0.403 to 0.716 for Normal copula, 0.373 to 0.628 for Plackett copula and 0.564 to 1.00 for T copula. Frank copula and Plackett copula had the best goodness of fit. Kendall’s tau for Frank copula showed a correlation of -0.4212. CONCLUSIONS: Copulas distribution allows us to adjust the non-linear relation between cost and effectiveness. Furthermore, this kind of approach could improve probabilistic sensitivity analyses.