PM41 A STUDY ON CYTGENETIC AND MOLECULAR ANALYSIS OF PRESENILIN 1 (PSEN1) GENE IN ALZHEIMER’S DISEASE
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OBJECTIVES: Alzheimer’s disease (AD), the most common form of dementia, is a degenerative brain disease that leads to cognitive loss. Oxidative stress is a hallmark of AD. This study aims to identify the genetic alterations of AD by using the conventional cytogenetic technique by Trypsin G-banding and molecular analysis of presenilin 1 (PSEN1) genotype by PCR. The role of selected ions related to energy metabolism such as a consequence of oxidative stress in the deterioration accompanied by AD patients were also analyzed. METHODS: The present study includes 49 AD patients and the subjects were categorized in two groups ([4 Early-Onset AD]) patients and ([31 Late- Onset AD]) patients, in order to investigate the possible cytogenetic and molecular changes. The gels were developed by staining with silver nitrate. RESULTS: The Late- Onset AD patient shows higher total CA level when compared to Early-Onset AD patient. A comparison of the frequency of the IRP5 genotypes among the Early-Onset AD and Late- Onset AD subjects demonstrated a significant difference between the two groups. CONCLUSIONS: The strong association of PSEN1 with Late- Onset AD patients called attention to the importance of genetic studies. Oxidative stress is a consequence of oxidative stress in the deterioration accompanied by AD patients. The Late- Onset AD patients show higher total CA level than the Early- Onset AD patients.

PM63 THE ACCEPTANCE OF MORBIDITY ENDPOINTS IN THE AMANO IN GERMANY–ARE THERE GREATER Hurdles FOR SUBSTANCES WITHIN ONCOLOGY
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Objective: The objective of this study is to assess the acceptance of morbidity endpoints by the Institute for Quality and Efficiency in Healthcare (IQWiG) within the early benefit assessment in Germany. The paper focuses on morbidity endpoints (ME) for oncology substances compared to non-oncology substances: (1) how many ME have been accepted? (2) In how many cases has IQWiG determined an additional benefit based on ME? METHODS: All benefit assessments published by the IQWiG between 01/01/2011 and 01/12/2017 were considered (n = 126). Of those, 80 were excluded from the analysis due to one of the following reasons: orphan drug designation, no dossier submitted or incomplete dossier due to missing basic data. The remaining 46 were used to calculate the number of accepted ME as proportion of all submitted endpoints; additional benefit based on accepted ME; percent of assessments in which at least one ME was accepted. RESULTS: In total, 19 oncology and 27 non-oncology assessments have been included into the analysis. For the 19 oncology assessments, a total of 76 ME had been submitted. IQWiG accepted hereof 20 ME (26%). Accepted ME include: pain, skeletal-related complications and symptoms. The IQWiG determined an additional benefit for six assessments based on ME (6/19=32%). For the 27 non-oncology assessments, 127 ME had been submitted. IQWiG accepted 79 (~62%) including: strokes, cardiovascular events and relapse-related events. For non-oncology substances, IQWiG determined an additional benefit for thirteen assessments based on ME (13/27=50%). At least one ME endpoint was accepted in 83% of oncology assessments and in 100% of benefit assessments in all other indications. CONCLUSIONS: Though the rate of accepting ME in oncology indications is numerically lower (32% vs. 48%), the difference does not reach statistical significance (p=0.36 Fisher’s exact test).

PM665 COMPARISON OF TREATMENT-RELATED ADVERSE EVENTS RECORDED IN ADMINISTRATIVE CLAIMS DATA WITH THOSE RECORDED IN ELECTRONIC MEDICAL RECORDS FOR MULTIPLE MYELOMA PATIENTS
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Objective: Objective was to compare adverse events (AEs) related to treatment with novel therapies or traditional chemotherapy observed in observational studies frequently used administrative claims data or electronic medical records (EMR) to assess potential AEs. The purpose of this analysis is to compare the occurrence of AEs identified in claims data with those recorded in an oncology EMR database (Endovex®) in Multiple Myeloma cases (n=278) treated with novel agents in a real-world setting. The study compared the occurrence of AEs as reported by claims (EMR) and EMR-Claims Linked Dataset who received novel or traditional chemotherapy were included. The index date was the first date of medication administration/order and patients were followed for AEs, including neutropenia, thrombocytopenia, venous thromboembolism (VTE) and diarrhea, until a > 90 gap in all medications for the first regimen. RESULTS: Neutropenia and thrombocytopenia were recorded less often in claims (neutropenia 9%; thrombocytopenia 7%) compared to EMR data (neutropenia 15%; thrombocytopenia 11%). Neutropenia and thrombocytopenia are monitored by oncologists with lab values and this may lead to more frequent recording of less severe AEs in the EMR not reflected in claims data. VTE and diarrhea were recorded less often in claims (VTE 4%, diarrhea 7%) compared to the EMR (VTE 4%, diarrhea 4%). A VTE diagnosis may likely result in hospitalization and patients with diarrhea may seek care outside of their oncology practice; hence, claims data may capture additional diagnoses assigned by clinicians other than oncologists. Overall, the highest proportions of AEs were found with the linked data containing Endovex® and claims data linked to EMR linked data. The most common AEs recorded by clinicians in settings outside the oncology practice were recorded more often in the claims data. The linked claims-EMR data provided the most complete assessment of potential treatment-related AEs.

PM66 NON-COMPARATIVE TRIALS TO SUPPLEMENT NETWORK META-ANALYSES USING ARM-SPECIFIC META-REGRESSION: AN APPLICATION TO COMBINATION THERAPIES IN HIV
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Objective: There is a growing call for the use of endonodal techniques within network meta-analyses (NMA), such as for informative priors or improved connectivity. Endonodal trials can also be used to further inform arm-specific meta-regression coefficients, which may be used to simplify node definitions in combination therapy. We applied this concept to a network of first-line antiretroviral therapy (ART) to determine efavirenz (EFV) versus nevirapine (NVP) in the presence of a boosted protease inhibitor (PI). We conducted a systematic search of electronic databases up to March 1, 2015. Nodes were defined as specific antivirals rather than ART regimens, which simplified endonodal trials can also be used to further inform arm-specific meta-regression used to adjust estimates accordingly. The alternative approach was to simply reduce the evidence base to trials that did not differ with respect to backbones. The most notable trial to differ in backbones was the SINGAPORE study comparing EFV vs. NVP (DTG) vs. EFV arms at 96 weeks. RESULTS: A total of 71 trials with 35,270 randomized patients informed the evidence base. DTG was found to be superior with respect to viral suppression at all time points (odds ratio [OR]: 1.87 a 48 weeks; 95% credible interval [Cr]: 1.34 – 2.64). Both DTG (OR: 0.26, 95% Cr: 0.15, 0.44) and low-dose EFV (OR: 0.39; 95% Cr: 0.17, 0.83)
tended to be protective of discontinuations due to adverse events relative to standard dose. Use of arm-specific regression supplemented by endomolar trials led to tighter confidence intervals facilitating decision-making. Specifically, DTG was consequently superior to EFV with respect to CD4 cell counts and ritelgravir was distinguishable from EFV when it was not otherwise. CONCLUSIONS: Making full use of all data from the focal treatment group, the model may only assume a progression degree of 0.2% as independent variables and the logit of progression degree as a dependent variable. RESULTS: 1,436 target patients were extracted from the database. When the actual progression degree is over 80%, the estimated progression degree rises with the actual degree, however, at the lower progression degrees, the estimated degree was excessively underestimated. CONCLUSIONS: We have developed a model to estimate progression degree of HTA. The model may only assume a progression degree well only for the last phase patients. The model should further be improved to minimize the bias at the lower degree.

PM12
BEYOND THE MIDDLE: EVALUATING SURROGACY OF CLINICAL TRIAL ENDPOINTS ACROSS TRIAL DURATIONS
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OBJECTIVES: Overall survival (OS) remains the gold standard measure of clinical value. However, due to its variability between diseases and treatments. However, given recent advances in treatments, and prolonged survival, OS benefits are becoming more challenging to establish, requiring more extensive follow-up. A number of methods to test this rationale have been developed. In this paper, we consider the effect of follow-up time on the evaluation of survival times. Patient populations between the clinical trials were comparable to one another. Statistical analysis was conducted in STATA 12. RESULTS: Correlation analysis found the strongest association between PFS and OS between 75% and 25% survival (0.865 to 0.953; p < 0.01), with a weak association at 90% survival (0.61; p = 0.096). Regression analysis also found that FFS had the largest influence on OS between 90% survival. CONCLUSIONS: We present the various aspects of how patients progress across and within types of therapies, it is essential to ensure the surrogacy of the endpoint across the full trial duration. For example, patients may progress early on in a disease and surrogacy may not be consistent across different time points. In conclusion, in the exploratory analysis, using this approach of scanning survival data will provide a richer picture of the disease area that may no longer be available from authors or research institutions.

PM13
NETWORK META-ANALYSIS OF MULTIPLE OUTCOMES INCORPORATING DOSE-RELATED CONSTRAINTS: APPLICATION TO OVERACTIVE BLADDER SYNDROME
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BACKGROUND: Overactive bladder(OAB) is characterized by symptoms of urgency, incontinence, frequency and nocturia. With the syndromic nature of the condition, clinical trials often solely report the most effective outcome i.e. the symptom with the largest improvement. As a result different interventions are evaluated for different outcomes, which can have severe implications for network meta-analyses, and ultimately decision-makers. METHODS: We developed a dose-related network meta-analysis(MVNA) to identify the most effective intervention for treating OAB syndrome. METHODS: Using Bayesian Markov Chain Monte Carlo methods, we developed MVA to generate the net odds ratio for the multiple outcomes to predict treatment effects for missing data. We extended this model to incorporate the exchangeability between treatment effects of the same intervention with different methods of administration (e.g. immediate release, extended release, enteric coated–etc.) and drug-dose–with a dose-maturity. The model was fitted to the data and compared to the initial model. The outcomes of interest were mean change from baseline in incontinence, and urgency episodes D; independently, the datasets included 109 and 56 trials, respectively. RESULTS: The model was fitted to the data and compared to the initial model. The results show that the initial model is not related to study relevant morbidity and that sample bias cannot be concluded. CONCLUSIONS: Careful follow-up methods guide to estimate high-loss-to-follow-up in long-term prospective studies of drug safety. Since drop-out cannot be attributed to study relevant confounders, attrition does not need to sample bias.

PM11
ESTIMATION OF THE PROGRESSION OF COLON CANCER BY JAPANESE LARGE-SCALE INSURANCE BENEFITS DATA ANALYSIS
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OBJECTIVES: Acute progression is a manifestation of the progression degree in colon cancer is of paramount importance for the decision making in treatment policy. However, it was difficult to extract the exact status from the real-world data. The objective of the study was to develop the model to determine the progression degree using the insurance benefits data in Japan. METHODS: We conducted analyses using claims data provided by Medical Data Vision Co., Ltd. We extracted target patients by the criteria those who meets all of the following conditions, at least one medical diagnosis code(JCd) C18-20, tractable from the first diagnosis to death, and have at least 365 days of observation. We set the progression degree as a scale from 0% to 100%. The degree of 100% indicates the patient death. For the first diagnosis, the scale was adjusted based on the patient's condition. We have developed a linear regression model by using the medication frequency of ATC codes as independent variables and the logit of progression degree as a dependent variable. RESULTS: 1,436 target patients were extracted from the database. When the actual progression degree is over 80%, the estimated progression degree rises with the actual degree, however, at the lower progression degrees, the estimated degree was excessively underestimated. CONCLUSIONS: We have developed a model to estimate progression degree of HTA. The model may only assume a progression degree well only for the last phase patients. The model should further be improved to minimize the bias at the lower degree.

PM10
DOES ATTRITION IN SUBJECT-BASED STUDIES OF DRUG SAFETY LEAD TO BIAS RELATED TO MORBIDITY?
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OBJECTIVES: Attrition bias in clinical studies is often omitted from HTA submissions. There is a need for cross communication between groups to reach a consensus on how to develop a suitable tool. Until a suitable tool is developed, reviewers should select the most appropriate checklist for the design of the studies identified in a particular SR.

PM9
CRITICAL APPRAISAL OF REAL WORLD EVIDENCE – A REVIEW OF RECOMMENDED AND COMMONLY USED TOOLS
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OBJECTIVES: In an absence of randomized controlled trials (RCTs) and to verify RCT evidence, the health technology assessment (HTA) agencies commonly rely on real world (RW) studies to provide efficacy evidence for healthcare interventions. RW study designs can introduce considerable bias into a systematic review (SR) and several methodologies exist to evaluate the risk of bias in such studies. We conducted a search to identify which tools are commonly used and which are recommended by HTA bodies. METHODS: A targeted search of SRs including RW studies, conducted in MEDLINE and EMBASE (OVID SP), identified reviews published January 2013-June 2015. Studies identified were reviewed to determine which appraisal tool was used. Secondly, recommendations for the critical appraisal of RW studies by expert review groups (Cochrane, CRD) and HTA bodies (NICE, SMC, NCPE, AWMSG, IQWiG, PBAC, AMCP, AHRQ and CADTH) were reviewed. RESULTS: 1885 studies were identified and screened. Commonly used tools included Downs & Black, Chamblee’s Newcastle-Ottawa Scale, and the CriStal checklist. Neither Cochrane nor CRD recommend a particular tool of bias instrument. The AHRQ developed the MORE checklist reviewing a wide variety of different critical appraisal tools. Of the other HTA bodies only CADTH recommend using a specific critical appraisal tool; SIGN 50 (for cohort or case-control studies). The tools identified examine a variety of criteria including reporting bias, funding bias, conflated analysis, and errors in the study results. AHRQ is no consensus on a preferred instrument that allows for the assessment of all types of RW evidence and critical appraisal of RW evidence is often omitted from HTA submissions. There is a need for cross communication between groups to reach a consensus on how to develop a suitable tool. Until a suitable tool is developed, reviewers should select the most appropriate checklist for the design of the studies identified in a particular SR.